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## ERRATA

Page 171, line 28, *delete* therefore

- „ 178, „ 33, *for* (Fig. 2). *read* (Fig. 1).
- „ 181, „ 3, *insert* (Fig. 5) *after* ganglion cells
- „ 181, „ 11, *insert* and *after* ganglion
- „ 189, „ 33, *for* (Fig. 4). *read* (Fig. 3).
- „ 209. DESCRIPTION OF PLATES:

Fig. 2, line 3, *for* vacuolation prominent. *read* vacuolation absent.

Fig. 10, *for what is printed read*—Section of corpus Luysii stained by Scharlach R. showing partial necrosis.  $\times 50$ : The portion enclosed by the square is reproduced in Fig. 11.

Fig. 14, Corpus Luysii showing intracapillary erythropoiesis  $\times 700$ .

Fig. 15, *insert* stained for fat. *after* Luysii

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THE RHYTHM OF PAROXYSMAL TACHYCARDIA<sup>1</sup>  
AN ELECTROCARDIOGRAPHIC STUDY

By A. U. MACKINNON  
(From the First Medical Clinic, Vienna)

With Plates 1 to 3

IN 1923 G. F. Strong and S. A. Levine (1) came to the conclusion—on the basis of two cases of paroxysmal ventricular tachycardia which they had studied—that ‘... the rhythm of the heart in ventricular tachycardia, although fairly regular, shows variations in the lengths of the cycles that are appreciable, often 0.1 second in consecutive cycles, and sometimes as high as 0.19 second. The average variation of consecutive beats in the two cases of ventricular tachycardia was over ten times as great as the average variation in cases of simple tachycardia. The arrhythmia can be detected by auscultation of the heart. It is suggested that this may help to distinguish clinically the ventricular from the auricular tachycardia...’ Although this generalization was based on the evidence of two cases only, and clinical irregularity had never previously been noted in the twenty or more published cases, it has been adopted without question into much of the recent literature on cardiology. Two notable examples are *Recent Advances in Cardiology* by T. East and C. W. C. Bain, p. 99, and P. D. White’s *Heart Disease*, pp. 635 and 641.

The conclusions arrived at in the present study are that the majority of cases of paroxysmal ventricular tachycardia are clinically regular; that clinical irregularity may occur in both auricular and ventricular tachycardias; and that its presence should, therefore, not be regarded as a point of distinction between the two conditions.

I. *The Regularity of Paroxysmal Ventricular Tachycardia*

Tables I and II show the figures obtained by examination of electrocardiographic records of sixteen cases of the Erste Medizinische Klinik (Wien), and twenty-two from the literature. In every case examined all the recognized electrocardiographic criteria of paroxysmal ventricular tachycardia were present and the diagnosis beyond dispute, i.e. (i) The individual paroxysms began and ended abruptly, and consisted of a series usually

<sup>1</sup> Received September 1, 1933.

regular—of ectopic ventricular beats; (ii) the first beat of each paroxysm was a premature ventricular contraction; (iii) if *P*-waves were visible they were independent of the ventricular rhythm, except in special cases where retrograde conduction from the ventricles occurred, when the auricular waves followed the ventricular complexes. The auricular complexes were usually normal in appearance, and their rate was slower than that of the ventricle. Rarely disturbances of auricular rhythm such as fibrillation or flutter were present; (iv) electrocardiograms taken before and after attacks frequently showed isolated ventricular extra-systoles of the same form as the ventricular complexes present in paroxysms; (v) supraventricular tachycardias in which intraventricular disturbances of conduction occur were always carefully excluded. In the majority of tracings examined the time-marker registered intervals of 0.04 second. The times have been accurately measured to the nearest 0.01 second, in some cases to the nearest 0.005 second.

These measurements, which are of consecutive ventricular cycles, have been made between the apices of the most sharply pointed deflections (usually R or S) of the ventricular complexes. Whenever possible, fifteen or more consecutive ventricular cycles were measured. Some of the figures, however, were derived from short records of three leads. In these seven or eight consecutive cycles in each lead were measured. Whether there was a change in rate between the leads or not, does not matter in regard to the point at issue, viz., to demonstrate the degree of irregularity between consecutive beats. When a change of rate (gradual or abrupt) was present the average variation time was not calculated.

In cases where the figures include cycles at the beginning and end of paroxysms, and where the first four or last two cycles are irregular, these times (which are underlined) have not been included in the calculations.

It is not claimed that the measurements can compare in minute accuracy to those made with a Lucas Comparator, but the degree of error is so slight as not to affect the main purpose of this paper.

The records of sixteen cases of paroxysmal ventricular tachycardia occurring in the I Med. Klinik were examined. In all but one of them, the maximum variation between consecutive ventricular cycles never exceeded 0.02 second. In ten the maximum variation was 0.01 second or less. In the exceptional case the maximum variation was as high as 0.03 second.

Of the twenty-two cases from the literature that were examined, in all but one—where the maximum consecutive variation was 0.25 second—the maximum consecutive variation was never more than 0.02 second. In ten cases it was 0.01 second.

In all the cases where a constant rate was present figures are given for what is termed the average variation time, i.e., the average of the variation of every cycle from the average cycle time. This gives an impression of the regularity of the whole series. As can be seen from the examination of the figures in both tables, consistent regularity was a feature of them all.

Table III shows the comparable figures for twelve typical cases of auricular

paroxysmal tachycardia chosen without special selection from the records of the I Med. Klinik.

*Discussion.* The strikingly important finding common to all the records of paroxysmal ventricular tachycardia examined is the high degree of regularity present. Of thirty-eight cases the maximum variation between consecutive beats in twenty cases was 0.01 second or less; in sixteen cases it was between 0.02 and 0.01 second; and in only two cases (0.025 second and 0.03 second) above 0.02 second. The average variation was never more than 0.009 second and usually about 0.005 second or less. The figures for the average variation are admittedly somewhat artificial—inasmuch as the original time measurements were in 0.01's of a second; but they serve a useful purpose in demonstrating the high degree of regularity present.

In a recent work on paroxysmal ventricular tachycardia by Froment (17), based on the study of about 100 cases, the majority derived from the literature, the author states that only occasional cases, from the various types of the disease, are clinically irregular. He considers that clinical irregularity and other supposedly distinguishing signs of this condition are uncommon, and that the diagnosis should only be made on positive electrocardiographic evidence.

After considering the degree of irregularity present in electrocardiographic records in cases that were also clinically irregular, and bearing in mind the fact that in rapid tachycardias of all kinds slight variations in the loudness of the heart sounds may be present and tend to produce an illusion of irregularity, the writer thinks that there must be at least a difference of from 0.08 to 0.10 second in the time of consecutive cardiac cycles before an average ear can detect irregularity. An experienced clinician with a musical ear might possibly suspect the presence of irregularity when the variation between consecutive beats was as little as 0.05 second. No one has as yet determined exactly how much this difference in the time of consecutive ventricular cycle must be before the observer appreciates that the rhythm is irregular.

## II. *Irregular Ventricular Rhythm in cases of Paroxysmal Auricular Tachycardia*

In occasional cases of auricular paroxysmal tachycardia the ventricular rhythm may be definitely irregular; an irregularity that may be perceptible clinically. The usual cause for this irregularity is defective conduction in the *a-v* bundle and its branches.

*Case 1.* A boy, aged 17 years, with an aortic incompetence and mitral stenosis and incompetence, was admitted to hospital with high fever and diarrhoea. There was considerable oedema of the lower extremities, the patient was dyspnoeic, cyanosis was marked and the liver was enlarged. He was found to be suffering from auricular paroxysmal tachycardia, with

irregular conduction from auricles to ventricles producing a clinically appreciable irregular ventricular rhythm. As the result of treatment with large doses of digitalis, the degree of block increased and the ventricular rate became slower. On the fifth day after admission to hospital the tachycardia stopped suddenly. The patient never had another attack and is now in good health.

No digitalis had been given to the patient prior to his admission to hospital.

*Electrocardiogram.* Plate 1, Fig. 1. The tracing shows a typical auricular paroxysmal tachycardia with an irregular ventricular rhythm. The first part of the tracing is quite regular. Suddenly the ventricular rate is halved, every second auricular stimulus failing to provoke a ventricular contraction. Throughout the tracing the auricular complexes are regular, the average auricular cycle being 0.495 second and the rate 121.2 per minute. The slow 2:1 ventricular rhythm is interrupted in the middle of the tracing, two successive auricular stimuli producing ventricular contractions. The *P-R* interval in the second of these complexes is prolonged (0.37 second).

Following the 2:1 rhythm occur three regular complexes in which the *P-R* interval lengthens progressively from 0.23 second, to 0.29 second, to 0.32 second. The next auricular stimulus is completely blocked. Ventricle follows auricle in the following cycle the *P-R* interval being short—0.21 second. The next auricular stimulus is blocked. The rest of the record shows a regular 1:1 rhythm.

The *R-R* intervals of the consecutive ventricular cycles are: 0.51, 0.50, 0.50, 0.535, 0.54, 0.91, 1.015, 0.605, 0.87, 0.99, 0.555, 0.53, 0.89, 0.97, 0.54, 0.505, 0.49, 0.50, 0.50, 0.49, 0.50 second.

*Case 2.* The patient was a woman, aged 45 years, who had for two years suffered from attacks of paroxysmal tachycardia of auricular origin. The attacks only lasted a few minutes, occurred at varying times and from varying causes, and were sometimes of daily occurrence. On admission to hospital she was found to have a fully compensated mitral valvular lesion (incompetence predominating). In many of her paroxysms the heart was found on auscultation to be slightly irregular. No digitalis had been given before the electrocardiograms shown were taken. The attacks were readily stopped by carotid pressure. Patient lived for several years after this illness.

*Electrocardiograms.* Plate 1, Fig. 2, and Plate 2, Fig. 3. Plate 1, Fig. 2, shows a record taken from middle of paroxysm. Plate 2, Fig. 3, shows a record of sudden stoppage of paroxysm caused by carotid pressure—establishing the paroxysmal nature of the tachycardia. The normal ventricular complexes indicate the supraventricular origin of the tachycardia.

Plate 1, Fig. 2. Ventricular rhythm is definitely irregular, 150.6 per minute. Times of consecutive ventricular cycles (*R-R* periods) are: 0.41, 0.345, 0.51, 0.33, 0.475, 0.335, 0.455, 0.34, 0.455, 0.335, 0.45, 0.34 second.

The maximum variation between consecutive ventricular cycles in this series is 0.18 second.

*Case 3.* The electrocardiogram is shown of the case of a woman of 35 years, with a mitral stenosis and incompetence who suffered from attacks of auricular paroxysmal tachycardia. The tracing (Plate 2, Fig. 4) shows an auricular tachycardia presenting variations in the form of the auricular complexes. The ventricular rhythm is definitely irregular, the greatest variations

between consecutive cycles being 0.155 second. The ventricular rate is 120.0 per minute.

Such tracings are considered to be due to irregular stimulus formation taking place from several different foci in the auricle.

*Discussion.* The ventricular irregularity in Case 1 is clearly due to disturbances of *a-v* conduction. The irregularity in the second case is almost certainly due to the same cause, but as the auricular complexes are buried this cannot be proved with certainty. These irregularities are due to exactly the same causes as operate in auricular flutter when varying degrees of *a-v* block develop. The third case showing variations in the auricular complex is analogous to those cases of ventricular tachycardia showing irregular and polymorphic electrocardiographic complexes and is probably due to the same causes.

Very slight variations in the *a-v* conduction time occur in every case of auricular paroxysmal tachycardia. When these variations become relatively large, irregularity of ventricular rhythm may be so great as to be audible. Clinical irregularity is usually due, however, to the presence of dropped beats, which usually occur irregularly.

The irregularity due to the presence of dropped beats is not so great as might be supposed, because the *a-v* conduction time of the cycle preceding the dropped beat is always prolonged, and shortened for the cycle following the dropped beat. Thus the interval between the two ventricular contractions before and after the dropped beat—is always less than twice the time of the average cycle.

The electrocardiogram of the first case shows this process quite clearly. The irregularity in the second case is most probably due to the same mechanism, but owing to the fact that the auricular complexes are buried, the matter is not susceptible to proof.

### III. *The Causes of Irregularity in Paroxysmal Ventricular Tachycardia*

Appreciable irregularity—of more than 0.1 second between consecutive beats—occurs in certain more or less well-defined types of the disease, and the probable causes of this irregularity can be grouped as follows:

*Group I.* Completely regular stimulus formation occurs from the ectopic focus in the ventricle, but disturbances of conduction are present between the focus and the ventricle and produce an irregular ventricular rhythm. This condition is analogous to the disturbances of *a-v* conduction which occur in auricular flutter and in certain cases of auricular paroxysmal tachycardia.

Because the conduction time between focus and ventricle is usually long before a dropped beat and short after one, the pause which occurs when a beat is dropped is rarely twice the heart cycle time. When the heart is beating, quickly-dropped beats due to this cause may only produce a slight irregularity.

*Group II.* Regular stimulus formation occurs from the ectopic ventricular focus, but periodically a stimulus remains unanswered either because the strength of the stimulus falls below the excitation threshold of the ventricle, or because the excitability of the ventricle is diminished by some cause.

In these cases the dropped beat produces a pause twice the length of the heart cycle time, and irregularity of rhythm in a paroxysm is more apparent than in the first group.

*Group III.* Irregular stimulus formation occurs. This may be due either (a) to the fact that stimuli arising from one focus are irregular in time, or (b) stimuli arise irregularly from more than one focus in the ventricle.

Both causes are probably present in the terminal stages of fatal cases, or those showing digitalis intoxication.

One or more of the above causes may be operative in a case at the same or at different times.

Notes and electrocardiograms are given of a case in which the irregularity is principally due to the first and second of the causes discussed above.

*Case IV.* A young man, aged 24 years, whilst playing football, suddenly became breathless and felt a slight pain in the chest. He was admitted to the I. Med. Klinik, where the only abnormality of the heart or other organs—otherwise perfectly healthy—was the presence of a continuous paroxysmal ventricular tachycardia of the type described by Gallavardin as 'extrasystolies ventriculaires à paroxysmes tachycardiques'. When large doses of digitalis or quinidine were given, the tachycardia was abolished; whenever these doses were diminished the tachycardia reappeared. On auscultation the rhythm of the heart was occasionally regular, but for the most part was definitely irregular.

This condition persisted intermittently for five years; and eventually under the stress of repeated paroxysms the heart dilated: a relative mitral and tricuspid incompetence developed, and the patient died of a typical congestive failure.

The post-mortem examination revealed dilatation and hypertrophy of the heart, but valves and myocardium were perfectly healthy.

Histological examination revealed no abnormality.

*Electrocardiograms.* Plate 2, Fig. 5, Lead III. The tracing shows the complexes of a paroxysmal ventricular tachycardia. Alternation in the form of the complexes is present: alternation in the time of the ventricular cycles is also present. The ventricular rate is 132.3 per minute.

No evidence of auricular activity can be seen.

This type of irregularity showing alternation was present continuously in electrocardiograms taken up to the time of the patient's death.

Such ventricular tachycardias showing alternation in the form of the electrocardiogram complexes are relatively common in the recorded cases of this condition. They may be associated with slight alternation in the time of the ventricular complexes, but in some cases are perfectly regular.

In many cases alternation is the result of digitalis therapy.

Plate 3, Fig. 6. Leads I, II, III. This tracing was taken some days later and presents a different appearance to that previously shown (Plate 2, Fig. 5). Similar electrocardiograms were taken up to time of patient's death.

In all three leads a normal complex is followed by what may be regarded

as a series of short groups of ventricular extra-systoles (two or three) or as a series of short tachycardias, the whole presenting the typical electrocardiographic picture of one of the well known types of paroxysmal ventricular tachycardia.

In Lead II the tachycardia is interrupted by a normal beat.

In Lead I, as an example, it is seen that the time interval between the two beats of each pair is from 0.405 to 0.415 second; the time interval between the second beat of each pair and the first of the succeeding pair is 0.71 to 0.835 second i.e., approximately double the interval between the individual beats of each pair. The ventricular rate is 98.5 per minute.

Such tracings can only be explained by the fact that now and then a stimulus coming from the ventricular focus fails to excite a ventricular contraction. In this case these dropped beats occur for the most part quite regularly, every third stimulus being unanswered. In other electrocardiograms of this patient fifteen to twenty beats occurred perfectly regularly (in paroxysms) before a dropped beat occurred. This irregularity is most probably due to the cause described in Group II: some of the stimuli—regularly emitted by one ventricular focus—are either below the threshold required for exciting the ventricle, or the ventricle itself occasionally fails to respond to the stimulus because for some reason or other its excitability is diminished.

Some tracings from this patient were used in K. F. Wenckebach and Winterberg's book: *Die Unregelmässige Herztätigkeit* (Case of Scherf and Winterberg). As Wenckebach and Winterberg originally pointed out, the significance of this case lies in the fact that it shows that a ventricular circus movement cannot be the underlying mechanism of paroxysmal ventricular tachycardia.

### Summary

1. The common type of paroxysmal ventricular tachycardia is markedly regular, and such irregularities as are present between consecutive beats are so slight as to be inappreciable by the human ear as departures from a regular rhythm.

Certain cases of auricular paroxysmal tachycardia may be clinically irregular. In the absence of the so-called Gallavardin's sign—the presence of a venous wave in the neck beating at a definitely slower rate than the ventricle—clinical irregularity in a typical paroxysmal tachycardia should not be held to indicate the presence of a ventricular origin until the electrocardiogram has proved the diagnosis beyond dispute.

2. As a general rule cases of auricular paroxysmal tachycardia have a greater degree of regularity than those tachycardias arising in the ventricle.

3. Irregularity in paroxysmal ventricular tachycardia may be due to (i) conduction disturbances between focus and ventricle; (ii) focal stimuli being either too weak to excite the ventricle, or ventricular excitability so diminished that the ventricle does not respond to normal stimuli; (iii) stimuli arising irregularly from a single focus; (iv) stimuli arising irregularly from more than one focus in the ventricle.

TABLE I

*Cases of Paroxysmal Ventricular Tachycardia. I Medizinische Klinik*

Case.	Time periods of consecutive ventricular cycles.	Average cycle.	Rate.	Maximum variation between 2 consecutive beats.	Average variation successive cycles.	Remarks.
A	0.48, 0.48, 0.48, 0.48, 0.48, 0.48, 0.48, 0.48, 0.48, 0.48, 0.48, 0.48, 0.48, 0.48.	0.48	125.0	0.00	0.00	ECG from middle of a paroxysm.
B	0.37, 0.30, 0.355, 0.355, 0.355, 0.355, 0.355, 0.355, 0.36, 0.36, 0.36, 0.36, 0.36, 0.36, 0.36, 0.36.	0.358	167.6	0.005	0.0024	ECG from beginning of paroxysm.
C	0.30, 0.28, 0.30, 0.32, 0.33, 0.33, 0.33, 0.33, 0.33, 0.34, 0.35, 0.34, 0.34, 0.36, 0.36, 0.36, 0.36, 0.35, 0.36, 0.37, 0.37, 0.36, 0.36, 0.36.	0.33- 0.36	179.1 to 166.6	0.02	—	Record of complete paroxysm. Note decrease in rate.
D	0.27, 0.25, 0.24, 0.24, 0.24, 0.24, 0.25, 0.25, 0.26, 0.24, 0.26, 0.25, 0.28, 0.25, 0.28, 0.25, 0.27, 0.25, 0.28, 0.25, 0.28, 0.25, 0.28, 0.25, 0.28, 0.25, 0.26, 0.28, 0.26.	0.24- 0.28	242.9 to 226.4	0.03	—	ECG from beginning of paroxysm. Decrease in rate. Alternation.
E	0.28, 0.28, 0.28, 0.28, 0.28, 0.28, 0.29, 0.28, 0.28, 0.28, 0.28, 0.28, 0.28, 0.28, 0.28, 0.29, 0.28.	0.2812	213.4	0.01	0.0021	Record of complete paroxysm.
F	0.26, 0.24, 0.23, 0.24, 0.24, 0.24, 0.24, 0.25, 0.24, 0.25, 0.25, 0.25, 0.25, 0.25, 0.25, 0.26, 0.26, 0.26, 0.26, 0.26, 0.28, 0.26, 0.28, 0.26, 0.28, 0.27, 0.28, 0.28, 0.28, 0.27.	0.24- 0.28	250 to 219.0	0.02	—	ECG from beginning of paroxysm. Decrease in rate.
G	0.39, 0.40, 0.39, 0.40, 0.39, 0.40, 0.39, 0.40, 0.39, 0.40, 0.39, 0.40, 0.40, 0.40, 0.39, 0.40, 0.39, 0.40, 0.40.	0.396	151.5	0.01	0.0048	ECG middle of paroxysm.
H	0.39, 0.38, 0.39, 0.40, 0.38, 0.40, 0.39, 0.39, 0.40, 0.40, 0.40, 0.40, 0.41, 0.42, 0.40, 0.39, 0.38, 0.42, 0.40, 0.43, 0.40. End.	0.395	151.6	0.02	0.0085	ECG shows end of paroxysm.
J	0.31, 0.32, 0.32, 0.31, 0.325, 0.315, 0.31, 0.32, 0.32, 0.32, 0.31, 0.32, 0.32, 0.315, 0.32, 0.32, 0.31, 0.31, 0.32.	0.3166	189.5	0.015	0.0045	Middle of paroxysm.
K	0.26, 0.27, 0.27, 0.26, 0.27, 0.27, 0.27, 0.26, 0.27, 0.26, 0.26, 0.26, 0.27, 0.27, 0.26, 0.26, 0.26, 0.27, 0.27, 0.26, 0.26.	0.265	226.4	0.01	0.005	Middle of paroxysm.
L	0.30, 0.30, 0.295, 0.30, 0.295, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30.	0.2994	200.6	0.005	0.001	Middle of paroxysm.

TABLE I (continued)

Case.	Time periods of consecutive ventricular cycles.	Average cycle.	Rate.	Maximum variation between 2 consecutive beats.	Average variation successive cycles.	Remarks.
M	0.205, 0.205, 0.205, 0.205, 0.205, 0.205, 0.205, 0.205, 0.21, 0.21, 0.21, 0.21, 0.205, 0.205, 0.21, 0.21.	0.206	290.3	0.005	0.002	From middle of paroxysm.
N	0.265, 0.26, 0.26, 0.26, 0.27, 0.265, 0.265, 0.265, 0.26, 0.265, 0.27, 0.265, 0.265, 0.265, 0.27, 0.26, 0.265, 0.26, 0.27, 0.26, 0.26.	0.264	227.2	0.01	0.003	From middle of paroxysm.
O	0.40, 0.405, 0.415, 0.415, 0.405, 0.415, 0.415, 0.41, 0.41, 0.415, 0.405, 0.43, 0.42, End.	0.41	146.3	0.01	0.0045	ECG shows end of paroxysm.
P	0.32, 0.32, 0.32, 0.32, 0.32, 0.315, 0.315, 0.325, 0.32, 0.32, 0.32, 0.32, 0.32, 0.32, 0.32, 0.32, 0.325.	0.32	187.5	0.01	0.001	From middle of paroxysm.
Q	Lead I: 0.47, 0.47, 0.47, 0.47, 0.48, 0.46, 0.47, 0.48. Lead II: 0.48, 0.47, 0.47, 0.48, 0.47, 0.47. Lead III: 0.47, 0.46, 0.47, 0.47, 0.47, 0.47.	0.471	127.3	0.02	0.0036	From middle of paroxysm.

TABLE II

*Cases of Paroxysmal Ventricular Tachycardia. From the Literature*

Case.	Time periods of consecutive ventricular cycles.	Time of average cycle.	Rate per minute.	Maximum variation between consecutive beats.	Average variation from.	Remarks.
I	Lead I: 0.33, 0.33, 0.33, 0.32, 0.33, 0.32, 0.33, 0.32. Lead II: 0.33, 0.33, 0.33, 0.32, 0.33, 0.33, 0.32, 0.33. Lead III: 0.33, 0.32, 0.33, 0.33, 0.32, 0.32, 0.33, 0.32.	0.326	184.0	0.01	0.0047	From middle of paroxysm. Case I. Robinson and Hermann (2).
II	Lead II: 0.32, 0.32, 0.32, 0.32, 0.32, 0.31, 0.32, 0.32, 0.33, 0.32, 0.32, 0.31, 0.32, 0.32, 0.31, 0.32, 0.33, 0.32, 0.32, 0.31, 0.33, 0.32.	0.3195	187.8	0.02	0.0035	From middle of paroxysm. Case II. Robinson and Hermann (2).
III	Lead I: 0.36, 0.35, 0.35, 0.36, 0.35, 0.34, 0.35, 0.35, 0.35. Lead II: 0.35, 0.35, 0.35, 0.34, 0.35, 0.35, 0.35. Lead III: 0.35, 0.35, 0.35, 0.35, 0.35, 0.36, 0.35, 0.36, 0.35, 0.36.	0.351	170.9	0.01	0.0033	From middle of paroxysm. Case III. Robinson and Hermann (2).

TABLE II (continued)

Case.	Time periods of consecutive ventricular cycles.	Time of average cycle.	Rate per-minute.	Maximum variation between consecutive beats.	Average variation from.	Remarks.
IV	Lead I: 0.26, 0.26, 0.27, 0.25, 0.27, 0.26, 0.26, 0.26, 0.27. Lead III: 0.26, 0.27, 0.26, 0.26, 0.27, 0.26, 0.26, 0.26, 0.27.	0.2625	228.2	0.02	0.0045	From middle of paroxysm. Case IV. Robinson and Hermann (2).
V	0.30, 0.30, 0.31, 0.32, 0.31, 0.31, 0.31, 0.32, 0.32, 0.31, 0.31, 0.32, 0.32, 0.30, 0.31, 0.31, 0.31, 0.32, 0.32.	0.313	191.7	0.02	0.006	From middle of paroxysm. L. Gallavardin (3).
VI	0.37, 0.38, 0.37, 0.37, 0.38, 0.37, 0.37, 0.38, 0.37, 0.37, 0.37, 0.38, 0.37, 0.37, 0.37, 0.36, 0.38, 0.37, 0.37, 0.37, 0.38, 0.37, 0.36, 0.36, 0.37, 0.37, 0.37, 0.37, 0.37.	0.3713	161.6	0.02	0.0043	From middle of a paroxysm. L. Gallavardin (4).
VII	0.33, 0.33, 0.33, 0.32, 0.33, 0.32, 0.32, 0.33, 0.34, 0.32, 0.33, 0.32, 0.34, 0.33, 0.32, 0.33, 0.33, 0.32, 0.34, 0.33.	0.328	182.9	0.02	0.0056	From middle of paroxysm. Singer and Winterberg (5).
VIII	0.39, 0.39, 0.39, 0.39, 0.39, 0.39, 0.39, 0.39, 0.39, 0.39, 0.39, 0.38, 0.39, 0.39, 0.39, 0.39, 0.39, 0.40, 0.40, 0.39, 0.40. End.	0.391	153.4	0.01	0.0026	To end of paroxysm. L. Gallavardin (6).
IX	Lead II: 0.44, 0.43, 0.43, 0.42, 0.43, 0.42, 0.42, 0.42, 0.42, 0.42, 0.44, 0.44, 0.44. Lead III: 0.41, 0.42, 0.41, 0.40, 0.40, 0.41, N, 0.40, 0.42, 0.42, 0.40, 0.41.	0.40- 0.44	150.0- 136.4	0.02	—	Middle of paroxysm. Shows increase in rate. Case I. W. D. Reid (7).
X	Lead I: 0.43, 0.43, 0.43, 0.42, 0.43, 0.43, 0.43, 0.43, 0.42, 0.43, 0.42, 0.42. Lead III: 0.42, 0.42, 0.43, 0.42, 0.42, 0.42, 0.42, 0.42, 0.42, 0.42, 0.42, 0.42.	0.4236	141.8	0.01	0.0046	From middle of paroxysm. Case II. W.D.Reid(7).
XI	Lead II: 0.37, 0.37, 0.37, 0.37, 0.36, 0.35, 0.36, 0.35, 0.37, 0.35, 0.36, 0.35, 0.36, 0.35, 0.34, 0.36, 0.34.	0.3575	167.8	0.02	0.0086	From middle of paroxysm. Case III. W. D. Reid (7).
XII	Lead III: 0.44, 0.44, 0.44, 0.44, 0.44, 0.44, 0.43, 0.43, 0.44, 0.43, 0.44, 0.44.	0.4375	137.1	0.01	0.0037	From middle of paroxysm. Case IV. W. D. Reid (7).
XIII	Lead I: 0.36, 0.35, 0.36, 0.36, 0.35, 0.36, 0.36, 0.36, 0.35, 0.36, 0.36, 0.36, 0.36. Lead III: 0.36, 0.35, 0.36, 0.36, 0.36, 0.35, 0.36, 0.35, 0.36, 0.36.	0.357	168.0	0.01	0.0042	From middle of paroxysm. Case V. W.D.Reid(7).

TABLE II (continued)

Case.	Time periods of consecutive ventricular cycles.	Time of average cycle.	Rate per minute.	Maximum variation between consecutive beats.	Average variation from.	Remarks.
XIV	Fig. 8: 0.41, 0.40, 0.40, 0.40, 0.40, 0.40, 0.40, 0.40, 0.40, 0.40, 0.41, 0.41. Fig. 9: 0.41, 0.41, 0.41, 0.40, 0.41, 0.41, 0.41, 0.41, 0.41, 0.40, 0.42, 0.40.	0.4054	148.0	0.02	0.0054	From middle of paroxysm. Butterfield and Hunt (8).
XV	Lead I: 0.32, 0.32, 0.31, 0.33, 0.32, 0.32, 0.32, 0.32, 0.30, 0.30, 0.31, 0.31, 0.31, 0.31. Lead II: 0.31, 0.31, 0.32, 0.32, 0.31, 0.31, 0.31, 0.32, 0.33, 0.31, 0.32, 0.31, 0.31, 0.30, 0.31, 0.31.	0.3136	191.3	0.02	0.0064	From middle of paroxysm. Case I. Wolferth and McMillan (9).
XVI	Lead II: 0.39, 0.36, 0.40, 0.39, 0.37, 0.36, 0.53, 0.39, 0.36. Lead III: 0.36, 0.36, 0.35, 0.35, 0.35, 0.35, 0.37, 0.35, 0.34, 0.35, 0.35, 0.34.	0.3516	170.6	0.02	0.0039	From the beginning of paroxysm. Much irregul. at beginning. Case II. Wolferth and McMillan (9).
XVII	0.44, 0.44, 0.44, 0.44, 0.44, 0.44, 0.44, 0.44, 0.45, End.	0.441	136.0	0.01	0.0018	ECG shows end of paroxysm. Case III. Wolferth and McMillan (9).
XVIII	Lead II: 0.395, 0.39, 0.375, 0.375, 0.37, 0.38, 0.375, 0.365, 0.375, 0.37, 0.37. Lower tracing: 0.41, 0.415, 0.40, 0.405, 0.40, 0.40, 0.395, 0.395, 0.395.	0.375	160.0	0.015	—	1st ECG from beginning of attack. 2nd ECG complete short paroxysm. McMillan and Bellett (10).
		0.402	149.2			
XIX	Lead III: 0.395, 0.39, 0.39, 0.39, 0.395, 0.40, 0.39, 0.39, 0.39. Lead III (another attack): 0.37, 0.38, 0.38, 0.38, 0.38, 0.38, 0.38, 0.37, 0.37.	0.392	153.0	0.01	0.003	From middle of paroxysm.
		0.376	159.5	0.01	0.004	From middle of paroxysm. Case VIII. Levine and Fulton (11).
XX	0.257, 0.198, 0.212, 0.237, 0.243, 0.243, 0.253, 0.245, 0.248, &c. Later in paroxysm: 0.27, 0.27, 0.27, 0.27, 0.27, 0.27, 0.27, 0.27, 0.27, 0.27, 0.27.	0.245	244.9	0.01	0.0039	From beginning of paroxysm.
		0.27	222.2	0.00	0.00	Middle of paroxysm. H. M. Marvin and White (12).
XXI	Lead I: 0.59, 0.59, 0.59, 0.59, 0.60. Lead II: 0.61, 0.61, 0.62, 0.61, 0.61. Lead III: 0.64, 0.64, 0.64, 0.64, 0.64.	0.59-0.64	101.7-93.7	0.01	—	From middle of paroxysm. Decrease in rate. Case III. Dieuaide and Davidson (13).
XII	Lead I: 0.35, 0.36, 0.35, 0.36, 0.35, 0.36, 0.36. Lead II: 0.36, 0.36, 0.36, 0.36, 0.35, 0.36, 0.36. Lead III: 0.36, 0.36, 0.36, 0.37, 0.36, 0.37.	0.359	164.3	0.01	0.0036	From middle of paroxysm. Marvin (14).

TABLE III

*Cases of Auricular Paroxysmal Tachycardia. I Medizinische Klinik*

Case.	Length of consecutive ventricular cycles.	Time of average cycle.	Rate per minute.	Maximum variation between consecutive cycles.	Average.	Remarks.
10	Lead I: 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, Lead II: 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30. Lead III: 0.30, 0.30, 0.30, 0.30, 0.30, 0.30.	0.30	200.0	0.00	0.00	From middle of paroxysm.
11	Lead I: 0.27, 0.27, 0.27, 0.27, 0.27, 0.27, 0.27, 0.27, Lead II: 0.27, 0.27, 0.27, 0.27, 0.27, 0.27, 0.27.	0.27025	222.1	0.005	0.0005	From middle of paroxysm.
C	0.35, 0.35, 0.345, 0.35, 0.35, 0.35, 0.35, 0.345, 0.355, 0.355, 0.35, 0.35, 0.35, 0.35, 0.345, 0.35, 0.35, 0.34, 0.35, 0.35, 0.35, 0.35.	0.349	171.9	0.01	0.002	From middle of paroxysm.
D	0.375, 0.375, 0.375, 0.38, 0.37, 0.375, 0.375, 0.37, 0.375, 0.37, 0.375, 0.375, 0.37, 0.37, 0.375, 0.375, 0.37, 0.375, 0.375, 0.375, 0.37, 0.375, 0.38, 0.375, 0.375.	0.37416	160.3	0.01	0.002	From middle of paroxysm.
E	0.265, 0.26, 0.265, 0.265, 0.26, 0.26, 0.26, 0.265, 0.265, 0.265, 0.26, 0.265, 0.255, 0.265, 0.26, 0.265, 0.26, 0.26, 0.265, 0.26, 0.26, 0.265, 0.265, 0.265, 0.26, 0.265, 0.265, 0.26, 0.26, 0.26, 0.26, 0.26, 0.26, 0.26, 0.265, 0.26.	0.2619	229.0	0.01	0.0025	From middle of paroxysm.
21	Lead I: 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.30, 0.29, 0.29, 0.30, 0.30, 0.30, 0.30, 0.29, 0.30.	0.298	201.3	0.01	0.0032	From middle of paroxysm.
12	0.23, 0.24, 0.23, 0.24, 0.24, 0.23, 0.24, 0.23, 0.24, 0.24, 0.24, 0.24, 0.23, 0.23, 0.24, 0.23, 0.24, 0.24.	0.2365	253.7	0.01	0.0045	From middle of paroxysm.
9	Lead I: 0.37, 0.37, 0.36, 0.37, 0.37, 0.36, 0.36, 0.36, Lead II: 0.36, 0.37, 0.37, 0.37, 0.37, 0.37, 0.36, 0.37, Lead III: 0.36, 0.36, 0.37, 0.37.	0.366	163.9	0.01	0.0048	From middle of paroxysm.
3	Lead I: 0.37, 0.37, 0.37, 0.37, 0.37, 0.38, 0.37, 0.38, 0.38, 0.37, 0.37, 0.38, Lead II: 0.38, 0.38, 0.37, 0.38, 0.38, 0.37, 0.38, 0.38.	0.375	160.0	0.01	0.005	From middle of paroxysm.

TABLE III (continued)

Case.	Length of consecutive ventricular cycles.	Time of average cycle.	Rate per minute.	Maximum variation between consecutive cycles.	Average.	Remarks.
A	0.385, 0.40, 0.40, 0.405, 0.405, 0.405, 0.41, 0.405, 0.415, 0.415, 0.41, 0.415, 0.42, 0.425, 0.425, 0.43, 0.42, 0.43, 0.43, End.	0.40-0.43	150 to 140.1	0.01	—	Complete paroxysm. Note gradual slowing.
B	0.395, 0.395, 0.395, 0.395, 0.395, 0.395, 0.40, 0.40, 0.395, 0.395, 0.40, 0.40, 0.40, 0.405, 0.405, 0.405, 0.41, 0.41, 0.41, 0.41, 0.42, 0.42, 0.405, 0.415, 0.41, 0.41, 0.42, 0.42, 0.42, 0.42, 0.42, 0.40, 0.42, 0.42, 0.415, 0.405, 0.41.	0.395-0.42	151.9 to 144.5	0.02	—	From beginning of paroxysm. Note decrease in rate.
F	0.275, 0.245, 0.245, 0.245, 0.245, 0.245, 0.245, 0.245, 0.255, 0.25, 0.255, 0.255, 0.25, 0.26, 0.255, 0.26, 0.26, 0.26, 0.26, 0.265, 0.27, 0.27, 0.275, 0.275, 0.30, 0.31, 0.30, 0.305, 0.31, 0.31, 0.31, 0.31.	0.245-0.31	244.9 to 193.5	0.025	—	From beginning of paroxysm. Note sudden decrease in rate towards end of series.

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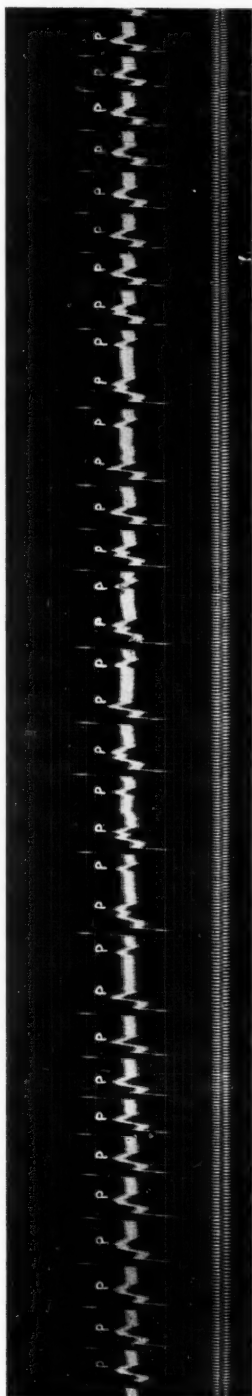


FIG. 1. Case 1. Auricular paroxysmal tachycardia with varying degrees of *a-v* block. Note 2:1 block; progressive lengthening of *P-R* interval leading up to a Wenckebach period. *P*-waves are perfectly regular. End of tracing shows restoration of normal sequential rhythm.



FIG. 2. Case 2. Auricular paroxysmal tachycardia with irregular ventricular rhythm, probably due to *a-v* conduction disturbances. *P*-waves hidden. From middle of paroxysm.





FIG. 3. Case, 2. From the same case, showing the abrupt finish of a paroxysm.



FIG. 4. Case 3. Auricular paroxysmal tachycardia, showing polymorphic auricular complexes. Ventricular rhythm is slightly irregular.

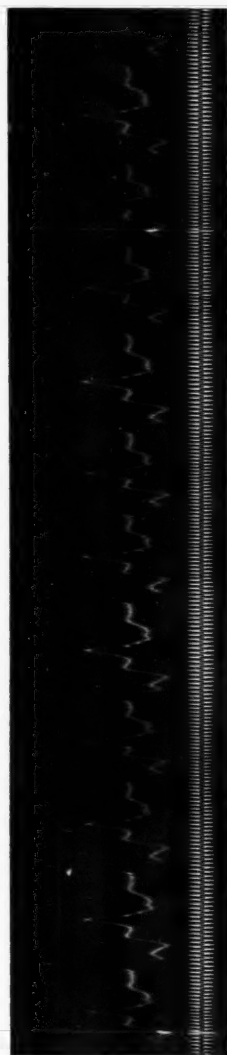


FIG. 5. Case 4. Paroxysmal ventricular tachycardia. Alternation in form and time of complexes present. P-waves hidden. Ventricular rate 132.3 per minute.



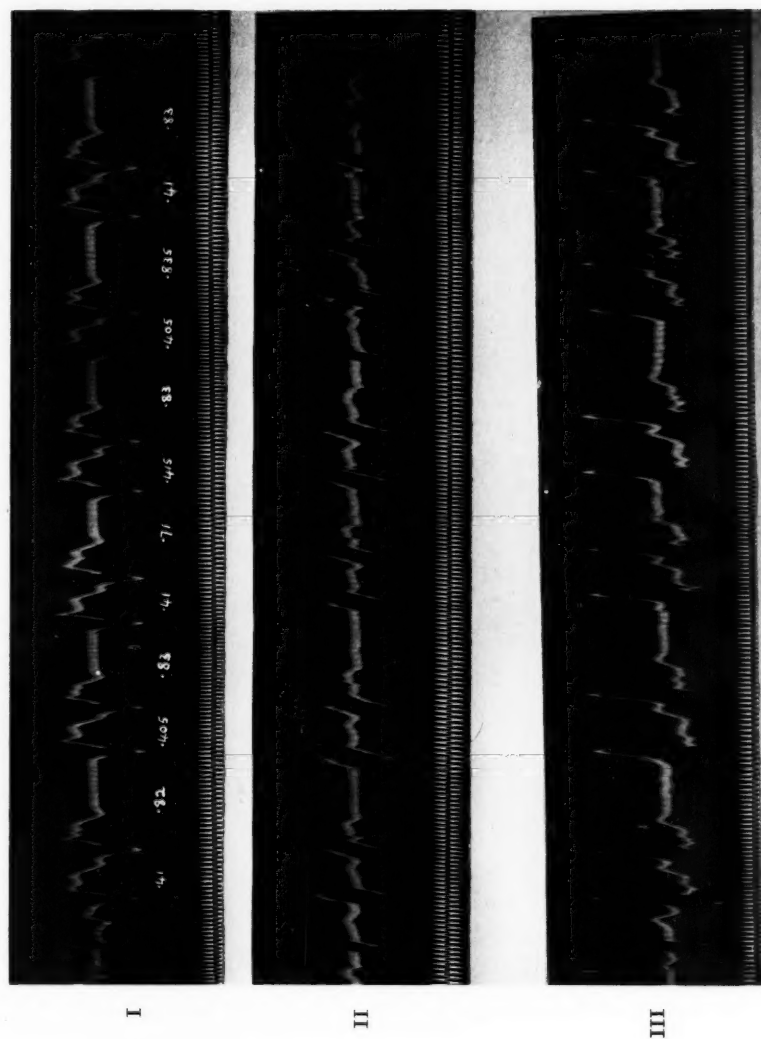
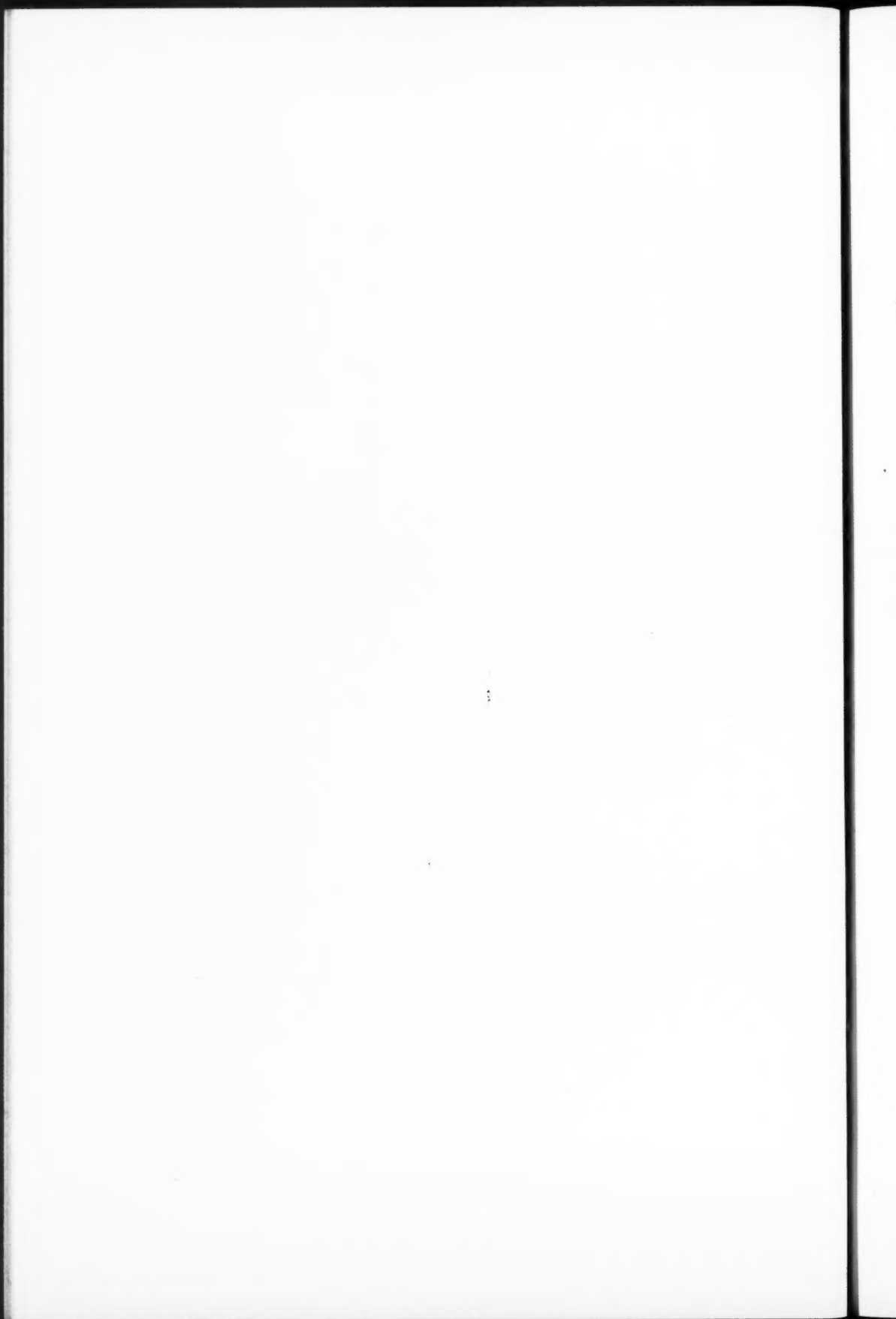


FIG. 6. Case 4. Leads I, II, and III. Paroxysmal ventricular tachycardia. The abnormal ventricular complexes are seen to occur in pairs; the time interval between each pair is nearly double the time between the members of each pair, i.e. probably every third impulse from the ectopic centre is blocked. In places normal complexes occur. Lead III shows the complete rhythm very clearly.



616.24-002.5

611.833.36

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## EVULSION OF THE PHRENIC NERVE IN THE TREATMENT OF PULMONARY TUBERCULOSIS<sup>1</sup>

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With Plates 4 to 7

THE primary aim in the treatment of tuberculosis is to obtain rest for the diseased part. In bone and joint tuberculosis immobilization is easily obtained, and with what beneficial results is well known, but phthisis presents a different problem as the lung is never, mechanically or physiologically, at rest. Various methods—artificial pneumothorax, thoracoplasty, and phrenic evulsion—of resting the diseased lung by producing a degree of collapse, are in use, and the value of the former two is already established. Induced paralysis of the diaphragm, however, used either alone or with other surgical measures, as a method of treating pulmonary tuberculosis, is of more recent origin, and there still exists some uncertainty as to the benefits likely to be derived from it. It is proposed to review a series of fifty-one cases, and to attempt to assess the value of, and the indications for, the operation.

### *The Function of the Diaphragm*

Although primarily the function of the diaphragm is not respiratory, but to raise intra-abdominal pressure (Jones (26)), it is as a respiratory organ that it chiefly concerns us, and only its function as such will be discussed. There is no doubt that the diaphragm, by increasing the intrathoracic negative pressure, is concerned to some extent in the aeration of all areas of the lung: whether it has a greater effect on one area than another is a debatable point.

Sir A. Keith (28, 29, 30, 31) has brought convincing evidence to show that apex of the lung, and particularly the posterior part of the apex, is largely dependent on diaphragmatic action for its proper aeration. Briscoe (11), although differing from Keith on certain details, was of a similar opinion, and

<sup>1</sup> Received July 28, 1933.

the importance of the diaphragm in expanding the apex has not been seriously disputed. The lung below is expanded by both costal and diaphragmatic action, and controversy has ranged chiefly round the question of what part each plays in their correlated action. Head (24) states that since the days of Galen there has been discussion as to the effect of contraction of the diaphragm on the movement of the ribs to which it is attached. Galen believed it raised them. Borelli and von Haller believed it tended to draw them towards the midline, and then in 1853 Duchenne produced what appeared to be convincing evidence in favour of the views of Galen. Keith (28), Briscoe (11), and Dally (18) all agreed with the original view of Duchenne that the action of the diaphragm on the lower ribs was to assist the external intercostal muscles in raising the ribs and widening the subcostal angle. Hoover (25) held that the action of the diaphragm was antagonistic to the external intercostal muscles, and that contraction of the diaphragm tended to pull the lower ribs towards the middle line and lessen the subcostal angle. He produced considerable experimental and clinical evidence in support of his opinions. Lemon (34, 35, 36) failed to confirm Hoover's findings, but most of his work was done on dogs, and he observed comparatively few cases of diaphragmatic paralysis in the human.

If Hoover's contentions are correct, a unilateral phrenicectomy ought to produce increased movement of the lower ribs and widening of the subcostal angle on the side of operation, as the restraining action of the diaphragm will be lost and the external intercostal muscles free to act. In this series thirty-two cases were carefully examined to see if any change in movement took place following evulsion of one phrenic nerve. In 50 per cent. of cases there was quite definite increased freedom of movement of the lower ribs and widening of the subcostal angle on the affected side: in the remainder the change was indefinite or absent, but in the majority of the latter cases there was extensive lung involvement with fairly marked contraction and fixation of the side. Where marked shrinkage and fixation of the chest is present, little change can be expected, and if it does occur the asymmetry of the chest makes detection of the change difficult. One may regard the figures that increased movement was present in 50 per cent. of cases as an understatement; actually it was present in the majority of cases where the pathological process was not too advanced or too chronic to prevent or obscure the change.

The clinical observations in this series lend support to Hoover's explanation of the action of the diaphragm. The fact that the apex of the lung relies largely for its proper aeration on free diaphragmatic movement, and the fact that the lung below the apex, which is expanded by both diaphragmatic and costal movement, receives some compensation by way of increased freedom of movement of the lower ribs following paralysis of the diaphragm, incline one to agree that a unilateral phrenic paralysis will produce a greater degree of rest of the apex of the lung than of other areas. This point will be again referred to in discussing the actual cases.

*Effects of Evulsion of the Phrenic Nerve*

The immediate effect of evulsion of the phrenic nerve is complete paralysis of the diaphragm on that side. The development of the costal portion of the diaphragm from the body wall (Keith (27)) points to the possibility of an intercostal nerve-supply as well, and has led to much uncertainty. Cavalié (15), Billard (9, 10), Schroeder (50), and Felix (quoted by Schlaepfer (49)), all concluded from their observations that there was an accessory motor nerve-supply from the intercostals, and Felix also described motor-fibres from the sympathetic. Morison (42) was also of opinion that there was double innervation. More recent workers, Schlaepfer (49), Kiss and Ballon (33), and Lemon (37) failed to find evidence of any motor nerve-supply other than the phrenic, and Lemon states that the work of Capps and Coleman can be accepted as conclusive evidence that the role of the lower intercostal nerves supplying the diaphragm is purely sensory.

One of our cases (No. 32) died six months after evulsion of the left phrenic nerve. *Post mortem* the paralysed left hemidiaphragm lay at a slightly higher level than the right, and the greyish-pink colour of the paralysed side contrasted markedly with the deep reddish-brown of the other. The change involved the whole of the left hemidiaphragm, starting abruptly in the mid-line and extending out to the costal margin. On cutting into the diaphragm, the atrophied side had shrunk to about one-quarter of the thickness of the normal side. Histologically, a section from the right hemidiaphragm showed normal muscle-bundles and nerve-twigs, while that from the left showed degeneration of muscle-cells and nerve-twigs, with marked increase of fibrous tissue. There was complete atrophy of the left hemidiaphragm, and the atrophy was limited exactly to this side: there was no evidence of cross-innervation or of an accessory nerve-supply from any source. Radiological examination of the diaphragm after evulsion of the phrenic nerve invariably shows a complete paralysis, and it may be accepted that the motor innervation of the diaphragm is solely by the phrenic, and the sensory by the phrenic and lower six intercostals.

Immediately on the evulsion of the phrenic nerve, the hemidiaphragm rises and takes up the position of expiration, being maintained there by the positive intra-abdominal and negative intrathoracic pressures. Its fixation is, however, only relative in that during inspiration it rises a little above the position of mean expiration, and during expiration falls a little below it. This so-called paradoxical movement, which can be readily seen on fluoroscopic examination, and was present in every case in this series in which the diaphragm was visible, is typical and diagnostic of phrenic paralysis. The writer has found, in agreement with most other workers, that the immediate rise is not necessarily maximum, but that the diaphragm may continue to rise for several months after operation. Accurate measurement of the amount of rise is difficult. Much depends on the depth of inspiration taken on successive radiograms. If after evulsion the patient does not take a full

inspiration at the time the radiogram is being taken, the rise will appear small. If he fails to do so at the taking of the radiogram previous to evulsion, he may fail to show the true position of the diaphragm which is to be paralysed, i.e. it may be fixed and raised by adhesions, and a false idea of the rise is thus presented.

Again, it is essential that the same position be used in successive radiograms, as a radiogram taken in the prone position shows the diaphragm at a considerably higher level than one taken in the upright. These facts may help to explain in part the difference obtained by various workers in the levels attained by the paralysed hemidiaphragm. In this series, on the right side, the greatest rise was 7.6 cm., the smallest 2 cm., and the average 4.9 cm.: the corresponding figures on the left were 7 cm., 2 cm., and 4.2 cm. It has been the general finding to get a higher average rise on the right, but there is no reason why this should be so. Davies (20) reports more cases showing a big rise on the left than on the right. Moore's (41) averages were: right 4.25 cm. and left 4.33 cm.

Wilson (54) declared that the patients of the hypersthenic type showed a greater rise of the paralysed hemidiaphragm than those who belonged to the asthenic type, largely due to the tonus of the abdominal muscles, and he had, by taking into consideration the tone of the muscles of the abdominal wall, the type of chest, and general condition of the patient, repeatedly been able to assess the height to which the diaphragm would rise. An examination of this series does not confirm this. In fact the patients exhibiting the greatest rises were of the asthenic type, and the writer is of the opinion that it is not possible to predict the degree of rise in any one case. Abolition of the inspiratory tug of the diaphragm and reduction of the size of the hemithorax results in a fall of the intrathoracic negative pressure, with a consequent relaxation of the elastic tension of the lung and shrinkage of the lung volume. The fall of the interthoracic negative pressure is felt equally by the whole of the lung surface, and a degree of relaxation of the whole lung therefore occurs. Where a lesion is fibrosing, the effect of the relaxation of elastic tension will be to increase its tendency to contract. After phrenic evulsion, the paralysed side of the diaphragm cannot do more than assume the position of expiration; and there is general agreement that the diaphragm may continue to rise for several months after evulsion. The writer has, by serial radiograms (Cases 18, 27, 33, 36, 48), frequently observed increased shrinkage of a fibrosing lesion proceed side by side with a gradually rising diaphragm. How far the gradual elevation is due to atrophy of the hemidiaphragm and easier displacement upward by the positive intra-abdominal pressure, and how far due to the increased shrinkage of a fibrosing lesion and reduction in lung volume, it is difficult to say. Probably both factors come into play, but the writer is of opinion that the latter is the determining factor in the ultimate height attained by the diaphragm.

The statement (Welles (53)) that the benefit derived from the operation is dependent on the height to which the diaphragm rises is not acceptable. Of

the cases in this series which showed a big rise, the majority certainly did very well, but they were all cases in which fibrotic change was established and in which marked shrinkage of the lesions took place: a few cases with a good rise did badly. The important factor is promotion of pulmonary rest and relaxation by abolishing diaphragmatic movement, and the ultimate height of the diaphragm may be regarded as an indication of the amount of contraction that has taken place in the lesion. Berard and Guilleminet (7) found the functional results were not proportional to the rise of the diaphragm, but they held that there must be immediate immobilization.

That cessation of movement is of primary importance does not necessarily mean that a diaphragm already raised and relatively fixed, is a contra-indication to operation, as has been held by some (Yates (56), Welles (53)). Aycock and Habliston (3) declared no result could be expected with a fixed diaphragm. In one instance (Case 23) the right diaphragm was 3.9 cm. above the left before evulsion, and showed no movement; after the operation it continued to rise, until finally it was 10.2 cm. above the left, and great shrinkage of the fibroid right upper lobe took place. A fixed diaphragm is not atonic, and the loss of tone and atrophy following evulsion of the phrenic nerve allows of further displacement upward.

#### *Changes in Circulation and Vital Capacity.*

Yates and Raine (57) pointed out that the reduction in volume of the lung following complete paralysis and atonicity of the diaphragm, when the rest of the diaphragm is not hindered by adhesions, approaches, but does not produce the position of collapse, and hold that under these conditions the lungs and pleura of animals with thick pleura, will receive the largest unit volumes of blood through the bronchial vessels, and the lungs the largest units of blood through the pulmonary vessels. It was experimentally shown in dogs by Andrus and Wilson (2) that, following unilateral phrenicotomy, there was an increase in pulse- and respiration-rate of 10 per cent., while the respiratory volume fell by 13 per cent., but the amount of blood flowing through the lungs was increased by 25 per cent., and compensation was established. O'Brien (44) held that the improvement of circulation was mainly in the contralateral lung. The reduction in lung volume varies with the height to which the paralysed hemidiaphragm rises. Bettman (8) gives the reduction as between 400 and 600 c.c., while Matson (38) declares that, according to Brunner's experiments, the reduction can scarcely amount to more than one-sixth to one-third of the lung volume, under the most favourable circumstances.

The actual reduction in vital capacity is considerably less than this. Wilson (54), in cases not complicated by artificial pneumothorax, found an average reduction of 311 c.c., or 18 per cent., and the reduction was least where the lung was extensively involved in disease. O'Brien (44), discussing artificial pneumothorax, points out that the vital capacity after inflation is

greater than the vital capacity before inflation minus the amount of air introduced. The reason is that the pulmonary tissue around tuberculous foci does not frequently participate in the aeration process, and collapse of these areas does not therefore affect the vital capacity. Just as in artificial pneumothorax collapse of a selective nature, and not compression, follows paralysis of the diaphragm, so that the degree of compensation required is not proportionate to the reduction in lung volume. Compensation is required for the normal lung tissue collapsed, and this appears to take place without any increase of respiratory labour, probably due to the improvement in circulation and more efficient utilization of the oxygen in the inspired air. O'Brien quotes Werner as finding a marked immediate drop in vital capacity in all patients, and a decrease in the tidal air in all but one patient, yet the oxygen consumption remained the same. In no case in this series was there any shortness of breath or increase in existing dyspnoea as a result of unilateral phrenic evulsion.

*Effect of Diaphragmatic Paralysis on Heart, Trachea, and Stomach.*

It is to be expected that some alteration in the position of the mediastinum will follow unilateral diaphragmatic paralysis, on account of the attachment of the pericardium to the diaphragm. Whether the upper part of the mediastinum is affected is, however, doubtful. The writer has not seen any noticeable change in the position of the trachea, although it is probable that where the trachea is pulled to one side by a fibrosing lung, paralysis of the diaphragm on that side, by relaxing the lung, will prevent further tracheal displacement.

Some displacement of the heart to the opposite side usually follows, but it is seldom marked and more noticeable on paralysis of the right than of the left hemidiaphragm: it practically never gives rise to symptoms.

Gastric disturbance occasionally follows the operation, but the symptoms are, as a rule, slight and transient and seldom call for treatment. Cooper (17) reports fairly marked gastric symptoms in five out of thirty-one cases, but his experience is unusual. Moore (41), out of sixty-three cases, had one patient who vomited for a week after left-sided phrenicectomy. Welles (53), in 300 cases, had few with digestive disturbances: most of them were temporary and no more common on left-sided paralysis than right. Ballon, Wilson, Singer, and Graham (5) investigated the question and tried to draw an analogy between eventration of the diaphragm and a high, paralysed diaphragm due to phrenic evulsion, but they decided that since phrenic evulsion had been performed so often without symptoms arising, that, as in cases of eventration, some hitherto unmentioned aetiological factor was necessary to precipitate symptoms. Air collecting in the stomach may fail to be expelled following a left phrenic evulsion, because of the loss of contractile power of the diaphragm, and may be sufficient to produce symptoms.

In this series only one man complained of epigastric discomfort and a feeling of fullness after food, following on a left phrenic evulsion with a big rise of the diaphragm, but the symptoms cleared up entirely in ten days. In no other case was there any complaint, and one may conclude that the operation has no noteworthy effect on gastric function.

#### *Operative Risks*

It was a result of the work of Davies (21), who described the anomalies of the phrenic nerve and the frequency of accessory phrenics, and thereby showed the reason for failure to get permanent paralysis following simple phrenicotomy, that the operation of phrenic evulsion came into general use. His work was confirmed by Kutamanoff and Ruhemann (Davies 20), and by Matson and Plenk (Matson 38). The latter workers, in 128 dissections, also observed that in five cases the accessory phrenic formed with the main branch a loop round the subclavian vein, and in two it formed a loop round the internal mammary artery, and thereby made us aware of one of the possible dangers of phrenic evulsion. Matson (38), from the German literature, gives many instances of accidents that have occurred in operation on the phrenic nerve, but most of these occurred in simple phrenicotomy and have the appearance of being due to faulty technique. Of more importance is the series of cases of death following phrenic evulsion that Berry (6) has collected from the literature, as these are illustrative of the chief dangers. These include cases of death from pyopneumothorax, from pneumothorax and mediastinal emphysema, from mediastinal haemorrhage, and from rupture of the pericardiophrenic artery.

The majority of these injuries can be avoided by careful operating, and large series of cases have been done by many surgeons without any accidents occurring. Rupture of the pericardiophrenic artery is not likely to occur in the living subject, as the nerve-fibres usually rupture before the tougher vessel wall. The frequency of a loop, formed by the junction of the main phrenic nerve with an accessory branch, encircling either the subclavian vein or the internal mammary artery has been mentioned, and the risk, although slight, of tearing either of these structures, is one that must be borne in mind. The passage of the accessory branch through the vein itself is a danger, but probably is very rare.

In cases where evulsion is not accomplished easily, the probability that the nerve is adherent at some point in its course through the thoracic cavity, and that an attempt to evulse it may lead to injury to vascular structures, or to tearing mediastinal or visceral pleura, or to rupture of a caseous gland, with risk of infection of the mediastinum or the formation of a pneumothorax or pyopneumothorax, must be reckoned with. Section of the nerve at as low a level as possible is advisable wherever undue resistance is encountered. This should certainly be done if an arterial tug is felt on the nerve while it is being pulled out. Transmitted pulsation was felt in two cases the writer has seen: both nerves were adherent and were cut as low

as possible, which was followed by complete and permanent paralysis. No untoward results were seen in fifty-one cases of evulsion.

Cases of reflex disturbance of the heart and circulation, shown by dyspnoea and pallor, with weak and irregular or rapid pulse have been reported by many operators. In a few of our cases pallor and increased pulse-rate have been present after the operation, but this quickly subsided, and no change was ever noticed in any patient that could not be attributed wholly to the mental upset attendant on a nerve operation under local analgesia.

#### *Indication for and Results of Phrenic Evulsion in Fifty-one Cases*

This series comprises fifty-one cases, which will be studied in three groups according as to whether the operation was done as a preliminary to thoracoplasty, in conjunction with artificial pneumothorax, or as an isolated procedure. In assessing the value of the operation, not only the ultimate results were taken into account: in many cases the outlook was hopeless, and in some of these the operation was done merely to alleviate symptoms, while in a few others it was nothing more than an attempt to help a patient who was getting progressively worse and in whom other methods of treatment were contra-indicated. The latter cases occurred early in the series, and with experience gained, cases of that type would not now be considered suitable. A truer estimate of the value of phrenic evulsion as a therapeutic measure in pulmonary tuberculosis will be arrived at by studying not only the ultimate results, but also individual cases as to whether or not the indications for operation were fulfilled. A fairly full table of indications and results has been included to avoid undue detail in the text.

*Phrenic evulsion as a preliminary to thoracoplasty.* This constitutes one of the most frequent indications for phrenic evulsion, and by many is employed as a routine procedure before every thoracoplasty. In three of the cases (10, 12, and 17), the operation cannot be described as anything other than a routine preliminary to thoracoplasty, to assist in giving a better collapse. No improvement was expected from the diaphragmatic paralysis alone, and in none could it be said that any special benefit was derived.

Davies (20, 22) and Wilson (54) state it should be done before every thoracoplasty, and this has been the generally accepted opinion. Recently, however, Davies (23) declared that he had changed his view: while he was still of the opinion that phrenic evulsion should be done as a preliminary in cases which were likely to require only a partial upper thoracoplasty, he did not advise it in cases which, from the nature or extent of the lesion, could be suitably dealt with only by the complete operation. In the latter, to paralyse the diaphragm was to produce a sodden, inert mass of lung; if phrenic evulsion were omitted, the diaphragmatic movement promoted a flow of blood and lymph and prevented complete stasis. On this point the writer has no personal experience, but on theoretical grounds there is much to be said for the view. Collapse would not be seriously inter-

ferred with, and the slight movement of the diaphragm, by improving circulation, would promote rather than retard healing.

The use of phrenic evulsion as a preliminary to thoracoplasty in doubtfully suitable cases, that it may improve the lung condition and the general condition of the patient sufficiently to allow of the major operation being safely undertaken later, has been widely advocated. Matson (38), Duma-rest (19), Davies (20), and others are all agreed on the benefits that can be derived from the operation in this connexion, Matson actually stating that the number of patients who improve sufficiently after phrenic evulsion to do without a thoracoplasty, alone justifies its use as a routine preliminary. Davies too, shows a big percentage that never required further operative treatment.

In six instances the operation was used with this end in view. Three of these (Nos. 3, 7, 13), all of which were very similar in that they had extensive fibrocaseous disease of one lung, and were febrile, improved sufficiently to have a thoracoplasty later, but in only one was the improvement at all marked. Of the remaining cases, two (Nos. 28 and 33) improved beyond anything that was expected, while in the other (No. 34) no benefit resulted. Of the former, one had a completely fibroid left lung with a huge upper lobe cavity, while the other had extensive very active disease of the right lung, and in this case, where improvement was slow but steady over many months, the ultimate result was so good that when last seen it was thought that thoracoplasty would be unnecessary. In the case which did badly, there was extensive, very active disease of the left lung: phrenic evulsion quite failed to influence it. Of two other cases which ultimately had a thoracoplasty with an excellent result, and in both of which the nerve had been evulsed primarily for relief of phrenic pain, one derived no special benefit from the evulsion beyond cessation of the pain, while the other was markedly improved. The added pulmonary rest and relaxation frequently results in a slow but progressive improvement, but it is impossible to forecast the result in any one case if there is any suspicion of activity. The result in one case may exceed anything that was hoped for, and in another the progressive nature of the disease may be quite unaltered. Phrenic evulsion certainly plays a most valuable part in preparing a patient for the major operation of thoracoplasty, but our experience is not altogether in keeping with Matson's. It must be granted that most of our cases were very extensively involved in disease, but it is just on these grounds that Matson's view can be disputed. There is a definite class of case in which the tuberculosis is mainly unilateral and where the lung is completely involved in dense disease. It is too much to hope that a paralysis of the diaphragm will produce any marked effect and it is just in this type, if the disease is not too active and the patient's general condition will allow it, that a complete thoracoplasty without preliminary phrenic evulsion may be advocated.

Paralysis of the diaphragm has also been advocated to assist thoracoplasty

the size of the hemithorax to that of the shrunken lung and tends to prevent old walled-off lesions being torn open.

A very similar indication is seen when progressive pleural symphysis with expansion of the lung tends to take place in the presence of a chronic effusion; Alexander (1), Baillis, Caussimon and Daydrien (4), and Moore (41) have all advised phrenic evulsion in such circumstances. Where there is a chronic effusion, which is usually purulent, the pleura is thick and the lung more or less fibroid; the progressive expansion by symphysis results in great contraction of the chest wall, and to paralyse the diaphragm not only reduces the size of the hemithorax, but by abolishing the inspiratory tug of the diaphragm, allows further contraction in a lung in which this is tending to take place, and gives the maximum of permanent collapse. Such cases would probably be preferably treated by thoracoplasty, but if there is any contra-indication to this, considerable benefit may be derived from the minor operation. This was done in four cases. In one case the expansion was very slow, and a year after the artificial pneumothorax was still being kept up with a fair collapse. In the other three complete obliteration of the A.P. space took place, but with the marked contraction of the chest on that side that followed and the diaphragmatic paralysis, a fair collapse was maintained and the patients remained well.

Phrenic evulsion is also of value in aiding collapse in a lung in which this is being hindered by adhesions between the lung and chest wall or diaphragm. The reduction of the inspiratory negative pressure and the abolition of the direct inspiratory tug of the diaphragm on the root of the lung, will increase the rest and collapse of the lung, and therefore give a certain amount of benefit, irrespective of the site of the adhesions. It has little direct effect on lateral adhesions, but apical adhesions are slightly relaxed. Its chief value is in cases where collapse is being hindered by adhesions from the base of the lung to the diaphragm. In one case (43) which had multiple adhesions, although collapse was slightly improved, the operation actually appeared to hasten the onset of a pleural symphysis. While maintaining that the chief beneficial factor in phrenic evulsion is cessation of movement, the result in cases of artificial pneumothorax with basal adhesions is influenced by the extent to which the diaphragm rises, and this is dependent on the intrapleural pressure. Where the pneumothorax is being maintained at a negative pressure a good rise can be anticipated, but if the pressure, is positive the beneficial effects are largely annulled by the diaphragm being pushed down and hindering relaxation of the adhesion. In one instance, a pressure of +1, +2, was sufficient largely to undo the benefit derived from the diaphragmatic paralysis.

The statement first made by Sauerbuch and Zadek, that fewer effusions occur in artificial pneumothorax after paralysing the diaphragm and that where effusions are present, the rate of formation of fluid is slowed up, is frequently encountered. Effusions in artificial pneumothorax are roughly of two types. They may be small, symptomless, and transitory or they

may be large and persistent. The former are due to pleural irritation (22) and tend to disappear spontaneously, and may never be seen unless by routine screen examination: the larger effusions, although occasionally they remain clear, more often become purulent and show little tendency to absorb. These are due to an actual tuberculous involvement of the pleura, and there does not appear to be any reason why a paralysis of the diaphragm should check these effusions. It may possibly check the rate of formation of the fluid by increasing pulmonary rest, but in none of our cases was there any appreciable difference. It must be remembered that, provided the fluid is removed as seldom as possible, the rate of re-accumulation gradually decreases, and it is difficult to judge if any change is produced by paralysing the diaphragm. In two instances, in both of which the nerve was evulsed on account of multiple adhesions interfering with collapse, an effusion followed after an interval with aggravation of symptoms and expansion of the lung.

Many authorities report a satisfactory lengthening of the interval between refills following the operation. This series is not suitable for investigating the question, as the majority of the cases were complicated by an effusion; refills in these cases were small and unaffected. In one other pleural symphysis was hastened and refills became small and difficult. Of the remaining cases, three in number, uncomplicated by an effusion at the time of evulsion of the nerve, in only one was there a satisfactory lengthening of the interval between refills. Both the others took as big and as frequent refills after operation as before, without any increase in pressure. Conclusions cannot be drawn from so small a number of cases. While it is reasonable to suppose the increased rest will retard the rate of absorption of air and that this, along with, in cases maintained at a negative pressure, the reduction in size of the hemithorax, may allow of spacing of refills, the advantage gained is not sufficient to warrant this alone as a suitable indication for evulsion of the phrenic nerve. It may be necessary later to do an artificial pneumothorax on the opposite side, and while a paralysed diaphragm on the initially diseased side does not absolutely contra-indicate this, it is a disadvantage.

Alexander and Zadec (quoted by Campbell (16)) advised that every artificial pneumothorax should be preceded by phrenicectomy on the grounds that more complete rest of the lung was obtained and that it checked effusions and lessened the frequency of refills. The last two points have already been discussed; it does not check effusions, and is of doubtful efficacy in reducing the frequency of refills. As regards the third advantage, it would be better to await the result of the pneumothorax before deciding whether more complete rest was necessary to control the disease, and if so, whether this could be obtained by paralysing the diaphragm. Again, an artificial pneumothorax may be necessary for the other lung. No advantage is gained by preceding a pneumothorax by a phrenic evulsion and it is not a justifiable procedure.

*Phrenic Evulsion as a Sole Operative Procedure*

Controversy has chiefly centred round the question of whether apical lesions derived the same benefit as basal from induced paralysis of the diaphragm, and while cases might be grouped and discussed according to the type of lesion, it is probably better to group them as far as possible according to site. That method will be followed here, together with a final group where the chief indication for operation was the relief of symptoms, and inevitably a few cases in this group will have been included in one of the others.

(a) *Cases in which lesions were predominantly basal (seven cases).* It will be seen from the table that the results were bad in four cases, very good in two, while the remaining case, in which paralysis was only temporary, was quite unchanged. Of those which did badly, three had advanced bilateral tuberculosis and were very ill, but in each active disease of the lower lobe was responsible for symptoms, and it was hoped to control this by paralysing the diaphragm. One derived no benefit at all: the other two improved temporarily but the progressive nature of the illness was unchecked. These cases, done early in the series, would not now be considered suitable for phrenic evulsion: they were too advanced and too active to hope for any great benefit. Although the disease in the fourth case was limited to the right lower lobe, phrenic evulsion failed to control it. By contrast, the remaining two cases (Nos. 30 and 39) did extremely well. In one, disease was largely fibrotic, but a big cavity was present in the right lower lobe; in the other, fibrotic change was in evidence, but there was a huge thin-walled cavity with a fluid level in the right lower lobe. The cavity in the first was greatly reduced in size, and in the second complete collapse of the basal disease and closure of the cavity resulted. While the results in two cases, where fibrotic change was established, exceeded expectations, the operation in the others where the lesions were active and exudative in character, failed to influence the course of the disease.

(b) *Predominantly upper lobe lesions (eleven cases).* In the majority more than the upper lobe was involved in tuberculous infection, and in most there was some involvement of the contralateral lung, but they are grouped under this heading as the part it was hoped to influence was situated in the upper lobe.

Cases 18, 21, 23, and 48 were very similar and reference to radiograms 13 to 16, which are from the first mentioned, will illustrate the course of events. In each there was fairly dense disease of the right upper lobe with cavities, which tended to become increasingly fibrotic, with contraction of the upper lobe and decrease in the size of the cavities. As fibrotic change advanced, the interlobar fissure became well defined and slightly concave downward. In all cases paralysis of the diaphragm was followed by progressive shrinkage of the upper lobe, which became small and fibroid. The cavities were greatly reduced in size, but never quite disappeared. The

results were uniformly good; that in two instances (Nos. 18 and 21), after the disease was apparently quiescent, active lesions should spring up in the opposite lung, does not negative the value of the operation in these cases, as in both, apparently inactive lesions were present in the contralateral lung at the time of evulsion of the nerve, and a long period elapsed before the lighting up of the disease in a fresh area.

In four cases big upper lobe cavities were present. Marked reduction in size followed in one, moderate reduction in another, while in the remaining two, in each of which a very big, thick-walled cavity lay in the upper lobe, very little change took place. Upper lobe involvement of a lighter fibrotic nature was present in two others; one had a group of small cavities at the right apex and the other had one large and several small cavities in the middle of the left upper lobe. Paralysis was followed by marked reduction in the size of the cavities in both instances. In all cases so far cited fibrotic change was either established or in evidence.

The last case of this sub-group indicates the opposite result. Although the disease radiographically had appeared to be becoming fibrotic, there were signs of fresh activity just before the phrenic nerve was evulsed. The result was disappointing, and beyond a slight temporary improvement the operation had no effect in controlling the disease.

*More extensive bilateral fibrotic or fibroid disease (six cases).* Three of these cases (Nos. 27, 36, and 49) were in many ways alike. All were admitted with extensive, bilateral, active tuberculosis, which, after a prolonged period in bed, steadily improved, and radiographically fibrotic change was in progress, as shown by pulling off the trachea and mediastinum to the more extensively involved side and pulling up of the diaphragm. Phrenic evulsion was done to allow of the maximum contraction in a lung where the process was already started. No marked immediate change occurred in any. Improvement was slow but steady, and the late result in every case excellent.

The remaining three cases were of densely fibroid disease. In one considerable reduction in the size of cavities at the apex and base followed, but the others derived no special benefit. In this type of case with very dense lung, shrunken chest, and thickened pleura, it is doubtful if it is worth while evulsing the phrenic nerve. The dense pleura prohibits any immediate further rise of the diaphragm: the diaphragm, being as a rule already pulled up and fixed to pleura, has practically no movement, and paralysing it produces very little change of note.

Campbell (16), Frimodt-Moller (40), Raycroft (48), Moore (41), and Thearle (52) all state that the principal use of phrenic evulsion alone is in control of lower lobe disease. Moore quotes Sergeant and Baumgartner as saying the effect is limited to the lower lobe. Davies (20) thinks that in basal tuberculosis there is considerable expectation that phrenic evulsion may arrest the disease, and Perret, Piguët, and Giraud (47) find it useful in basal lesions where there are signs of cicatricial retractile sclerosis.

The earlier opinions that diaphragmatic paralysis was principally of use in

controlling basal tuberculosis, largely arose from the idea that the diaphragm was chiefly concerned in expansion of the lower lobe, and that, following paralysis, the rising diaphragm compressed the disease in this area. The view has already been expressed that, since the posterior part of the apex is largely reliant on free diaphragmatic movement for its proper aeration and paralysis of the diaphragm is followed by increased freedom of movement of the lower ribs, there will be a greater degree of rest at the apex than elsewhere, following phrenic evulsion, and we might justifiably expect a better result in the treatment of apical than basal lesions. It is doubtful, however, if the increased costal movement is sufficient to be of any importance.

While admitting that, following diaphragmatic paralysis, pulmonary rest is probably greatest in the upper areas of the lung, the writer is of the opinion that the type of lesion is much more important than the site. Wherever a lesion is tending to fibrose, the contraction naturally tending to take place around it is hindered by thoracic and diaphragmatic movements. As soon as the diaphragmatic movements are abolished, retraction can take place. The opinion has already been expressed that cessation of movement of the diaphragm is the important factor and not the rise: paralysis is followed by a general relaxation of the lung and selective collapse of the diseased areas. If the disease is of the massive, exudative type, it derives some benefit from the added rest, but it does not tend to contract.

Tapie (51), Burnand (13), Oeckonomopoulos (46), and Wolf (55), agreed in finding the best results in upper lobe lesions with a tendency to fibrose. Dumarest and Berard (19), and O'Brien (45) were of the opinion that the result depended, not on the location of the lesion, but almost solely on its ability for spontaneous contraction. Cooper (17) noted apical and basal lesions equally affected. The writer's experience is in keeping with that of O'Brien, Cooper, and Dumarest and Berard. All the cases which improved as a result of phrenic evulsion were patients with a good resistance, in whom the disease was showing a tendency to fibrosis and contraction. Upper and lower lobe lesions appear to be equally benefited, provided these lesions are of a productive nature with little tendency to activity. Active lesions, whether apical or basal, did badly. In the acute caseating febrile type the chances of success are small, and phrenic evulsion should be avoided, although occasionally, as in Case No. 33, an unexpected excellent result is gained.

O'Brien (43) recommends phrenic evulsion in preference to artificial pneumothorax for the old fan-like lesions of the apex, with or without cavities, and for soft-walled cavities where the disease is tending to heal. In cases of the type shown in X-Rays 13 to 16, as much benefit is likely to be derived from phrenic evulsion as artificial pneumothorax. Even if artificial pneumothorax had been induced, the upper lobe would almost certainly have been adherent, and efficient collapse impossible (as happened in one instance—No. 37) and phrenic evulsion is probably preferable. Where

an active lesion has cleared up and left small cavities (as in No. 40), a phrenic evulsion may be all that is required to procure closure of the cavities. Bezançon's description (quoted by Bard (58)) that 'phrenic evulsion has as its unique end the object of allowing pulmonary lesions to follow the retraction already commenced' just about limits the scope of the operation as a primary choice. Where there is any suspicion of activity, the results of diaphragmatic paralysis are too uncertain to warrant its use instead of artificial pneumothorax. It is then to be used only when artificial pneumothorax has failed or is contra-indicated, as it is almost impossible to predict in any one case what the result of the operation will be.

The question of how far adhesions interfere with the efficacy of phrenic evulsion is one on which there is much difference of opinion. Alexander (1) and Yates and Raine (57) both think phrenic evulsion useless for upper lobe lesions if there are adhesions over the middle or lower lobes, but with this the writer cannot agree. The abolition of the inspiratory tug of the diaphragm and the general relaxation will be appreciated in the upper lobe, whether the lower lobe is adherent or not. Cases 22, 23, 38, and 48 were all cases of upper lobe disease in which an artificial pneumothorax had been unsuccessfully attempted. Several punctures were made in each case, not only over the upper but over the lower lobe, and no free space could be found, showing that the lower lobe was adherent. Yet, in every case, phrenic evulsion was followed by a good rise of the diaphragm, with, in three instances, a very good result. Nor does he agree with the statement (Bordet, quoted by Wolf (55)) that a thickened and adherent upper interlobar septum prevents diaphragmatic paralysis having a beneficial effect on the upper lobe. When this occurs, as was seen in several of our cases (e.g. Nos. 41 and 45) the retraction of the upper lobe results in a deformity of the septum: it becomes pulled up in the centre, forming an arc concave downward. Following phrenic evulsion, further contraction of the upper lobe does take place, the deformity of the septum increasing, and a good result can be obtained in spite of the symphysis. Wolf and Dumarest and Berard agreed that it was no contra-indication, the majority of the former's cases which were reported as improved or cured, having a total pleural symphysis.

#### *Effect of Phrenic Evulsion on Symptoms*

A careful note was kept of the effect of the operation on cough, ease of expectoration, amount of sputum, and temperature in every case. It was found that there was expectation of improving cough and expectoration in about 65 per cent. of those in whom it was troublesome. Easier expectoration is usually appreciated immediately in the majority of cases, and cough may be less even if there is temporary increase in the amount of sputum. A period when the patient experiences little change then ensues. In a favourable case, as the weeks pass, and the lung condition improves, temperature, if

previously raised, falls, the amount of sputum decreases, and consequently cough and expectoration become less. Cases which did badly showed either no change or a rise in temperature and an increase in the amount of sputum. The change in character of the sputum by the decrease of the purulent element, is probably a better index of the progress of the case. In cases treated by phrenic evulsion alone, the operation did not appear to have any effect on the presence or absence of tubercle bacilli in the sputum.

In twelve cases the primary indication for the operation was for relief of symptoms. The uses of phrenic evulsion in this connexion are many, but probably the commonest is to relieve difficult expectoration and troublesome cough. The abolition of the normal diaphragmatic resistance allows the powerful expulsive efforts of the abdominal muscles to be transmitted directly to the lung, and easier expectoration results. In eight of the cases this was the end in view. All had advanced fairly chronic fibrocaseous disease with cavities, in all cough was severe and distressing, and in four instances the efforts to empty the cavities in the morning almost invariably caused vomiting. After evulsion of the phrenic nerve, cough was less and expectoration easier in every case, and vomiting ceased. The amount of ease derived from the operation in cases in which vomiting is associated with a harassing cough, justifies it even in a patient in whom there is no hope of arresting the disease.

In two cases the operation was for relief of phrenic pain: pain ceased in both and thoracoplasty was done later with excellent results.

The remaining two cases had paralysis of the diaphragm induced in an attempt to control the haemorrhage. In one patient, who had very active disease of the whole of the left lung, with a huge upper lobe cavity, and who had had several large haemoptyses, phrenic evulsion was done only after an attempt at artificial pneumothorax had failed, but it had no effect in controlling the bleeding. Bleeding in the other case was much less profuse, and came from a large chronic cavity in the right upper lobe. Paralysing the diaphragm caused it to cease almost immediately.

O'Brien (43), Yates (56), Matson (38), and Wilson (54) have all reported success in controlling haemoptysis, and Miller (39) found the most frequent indication for phrenic evulsion was to assist other methods in controlling haemoptysis. Campbell (16) thought it was more likely to be successful if the bleeding came from the lower lobe. Yates and Raine (57) declared that haemorrhage from the pulmonary artery was readily controlled, but haemorrhage from the bronchial arteries was unaffected. It was not possible to express any view when only two cases had been done, but where an attempt to induce a pneumothorax has failed, and haemorrhage is not ceasing, phrenic evulsion is certainly a reasonable procedure.

*Summary*

Of the fifty-one cases, when last heard of, twenty-three were then alive and well, eleven others were alive, but the outlook in these was still doubtful: sixteen were dead and one dying.

If the series is viewed from the point of view as to whether or not the indication for operation was fulfilled, it is seen that in thirty-six instances the indication was definitely fulfilled, in four it was doubtfully fulfilled, and in eleven not at all. Where no definite indication for operation existed, no change took place.

Phrenic evulsion, whether used as a sole operative procedure or in conjunction with other methods of pulmonary collapse, has a somewhat limited, but still definite and valuable, place in the treatment of pulmonary tuberculosis.

In conclusion the writer wishes to express his indebtedness to Dr. C. Cameron, Medical Superintendent, East Fortune Sanatorium, for giving permission and providing facilities for the investigation, and for his constant interest and guidance in the work.

TABLE I. *Phrenic Evulsion, Preliminary to Thoracoplasty*

No.	Indication for phrenic evulsion.	Date of evulsion.	Length of nerve.	Rise of diaph.	Result.	Indication fulfilled or not.	End. result.
3	Fibrocaceous disease of whole of right lung: fairly dense perihilar fibrosis of left. Hoped for sufficient improvement after phrenic evulsion to allow of thoracoplasty being done.	9.1.29	25 cm.	?	Improved sufficiently to have thoracoplasty. She was a bad subject for thoracoplasty, but it was her only hope.	Fulfilled.	Developed secondary spread to left lung: intestinal tuberculosis. Died.
5	Left spontaneous pneumothorax: effusion developed which became purulent (streptococcal). Pyogenic abscess was to result and phrenic evulsion was done preliminary to thoracoplasty to attempt to reduce the size of the pneumothorax space.	27.5.29	12 cm.	Diaph. depressed.	No reduction in pneumothorax space followed: diaphragm pushed down by weight of pus.	Not fulfilled.	Died 1 hour after first stage thoracoplasty.
7	Dense fibrocaceous disease of whole of left lung. Right lung healthy. Phrenic evulsion merely preliminary to thoracoplasty.	27.5.29	27 cm.	?	Improved slightly. Thoracoplasty done with excellent result.	Fulfilled.	Alive and well (1.10.32).
8	Left A. P.—effusion and ultimate obliteration of A. P. Whole of left lung became fibroid: right healthy. He developed severe phrenic pain. Evulsion (1) primarily to relieve phrenic pain, (2) preliminary to thoracoplasty.	16.1.30	1 cm.	4 cm.	(1) Pain ceased, (2) he improved generally and thoracoplasty done with excellent result.	Fulfilled.	Alive and well (1.10.32).

9	Diffuse fibrotic disease of left lung: still active in lower lobe. Right lung healthy. Phrenic evulsion (1) primarily to relieve severe phrenic pain, (2) thoracoplasty was in view.	30.1.30	14 cm.	5.5 cm.	Pain ceased. An A.P. was later induced—partial and obliterated by effusion. Thoracoplasty done.	Fulfilled.	Alive and well (1.10.32).
10	Dense fibrocaceous disease of whole of right lung. Left lung relatively healthy A.P. impossible. Phrenic evulsion merely preliminary to thoracoplasty.	5.6.30	21 cm.	?	No change noticed in interval between phrenic evulsion and thoracoplasty (16.6.30).	Fulfilled.	Died shortly after second stage thoracoplasty from cardiac failure.
12	Completely fibroid left lung with upper lobe cavitation. Right lung showed perihilar fibrosis. A. P. impossible. Phrenic evulsion merely preliminary to thoracoplasty. Not expected to effect any improvement by itself.	25.8.30	—	4 cm.	She derived no special benefit from the phrenic evulsion. Thoracoplasty done 13.9.30.	Fulfilled.	Alive and well (1.10.32).
13	Dense fibrocaceous disease of the whole of the left lung. Some fibrotic disease of right. Phrenic evulsion to give sufficient improvement to allow thoracoplasty to be safely undertaken.	3.11.30	29 cm.	3.5 cm.	Cough less severe: sputum decreased. Improved symptomatically. General condition improved sufficiently to allow of thoracoplasty.	Fulfilled.	1.10.32. Alive and fairly well. Outlook doubtful—spread to right lung has taken place.
17	Dense fibroid disease of whole of left lung with multiple cavities. Right lung relatively healthy. Phrenic merely preliminary to thoracoplasty.	7.5.31	17 cm.	3.5 cm.	No apparent clinical benefit and thoracoplasty done 25.5.31.	?	Improved generally: on 1.10.32 alive and fairly well but outlook doubtful. The left lung became displaced and a good collapse was not obtained.

TABLE I (continued)

No.	Indication for phrenic evulsion.	Date of evulsion.	Length of nerve.	Rise of diaph.	Result.	Indication fulfilled or not.	End. result.
28	Completely fibroid left lung with huge upper lobe cavity. Good deal of fine nodular disease of upper half of right lung. Phrenic evulsion to give sufficient improvement for thoracoplasty to be undertaken.	17.9.31	11.5 cm.	?	Result excellent. She became afebrile, cough and spit disappeared, and the left lung became quite dry.	Fulfilled.	She left against advice and refused thoracoplasty. Permanent benefit could not be expected from phrenic evulsion alone. Broke down at home and died.
33	Dense disease of upper two-thirds of right lung of great activity. Restricted apical disease of left lung. A. P. attempted—no space. Phrenic evulsion with view to thoracoplasty if she improved sufficiently.	1.12.31	36 cm.	5.2 cm.	Slow but steady improvement followed. Temperature became normal, sputum decreased. Lung signs became dry and radiographically, after 6 months, fibrotic change was in evidence.	Fulfilled.	1.10.32. Further improvement and thoracoplasty may not be necessary.
34	Dense active disease of whole of left lung with a huge upper lobe cavity. Right lung healthy. Severe haemoptysis. Phrenic evulsion (1) as A. P. had failed, in an attempt to control haemoptysis, (2) if she improved sufficiently, for thoracoplasty.	3.2.32	10 cm.	No re-X-ray	(1) Quite failed to control haemorrhage, (2) effected no improvement whatever.	Not fulfilled.	Died.
44	Right localized apical pyo-pneumothorax with fine miliary, apparently healed disease, of the lung below and of most of the left lung. Partial thoracoplasty advisable. Preliminary phrenic evulsion (1) to effect possibly symptomatic improvement, (2) to test the stability of the left lung.	25.4.32	24 cm.	3.6 cm.	The phrenic evulsion was not expected to influence the pyo-pneumothorax. There was no change at all in his condition, clinically or otherwise.	Not fulfilled.	1.10.32. Condition unchanged; generally fairly well. Thoracoplasty not done.

TABLE II. Phrenic Evulsion in Conjunction with Artificial Pneumothorax

No.	Indication.	Date.	Length of diaph.	Rise of diaph.	Result.	Indication fulfilled or not.	End. result.
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TABLE II. *Phrenic Evulsion in Conjunction with Artificial Pneumothorax*

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No.	Indication.	Date.	Length of nerve.	Rise of diaph.	Result.	Indication fulfilled or not.	End. result.
14	Incomplete collapse of left lung—developed purulent effusion with progressive expansion of lung. Phrenic evulsion to reduce the size of the hemithorax and give the maximum collapse.	3.11.30	35 cm.	?	Diaphragm at first cupped down by effusion: absorption of air and fluid took place, followed by total symphysis with contraction of hemithorax and pulling up of the diaphragm. Greatly improved.	Fulfilled.	30.7.32. Alive and fairly well. Left lung completely fibroid with great contraction of that side of the chest.
15	Left A. P. induced for dense active disease of left lung: central spread in right lung. A. P. only partial—effusion and lung allowed to re-expand. Phrenic evulsion done to give a degree of collapse to the more extensively diseased lung. Little was hoped for and it was really done to please the patient.	5.1.31	18 cm.	2.5 cm.	There was no improvement in his condition: the disease steadily advanced. He was not a suitable case.	Not fulfilled.	Died.
19	Left A. P.—effusion and complete collapse followed by signs of expansion of the lung under the fluid. Phrenic evulsion (1) to give maximum collapse should symphysis take place, (2) to delay the rate of formation of the fluid.	18.6.31	8 cm.	2.5 cm.	(1) Degree of collapse increased, (2) diaphragmatic paralysis did not appear to affect the rate of formation of fluid.	(1) Fulfilled in that collapse increase and symphysis will take place at higher level if the lung creeps right out. (2) Not fulfilled as regards slowing up the rate of formation of fluid.	31.7.32. Generally very well. Expansion of the lung has been slow and collapse is still fairly good. Lung now crept out more than half way along the diaphragm.
29	Left A. P.—partial and developed effusion with progressive pleural symphysis and reduction of size of A. P. space. Phrenic evulsion to reduce the size of the hemithorax and give as much collapse as possible when the lung completely re-expanded. Condition of right lung precluded thoracoplasty.	5.10.31	21 cm.	2.2 cm.	Progressive symphysis took place with contraction of the hemithorax and pulling up of the diaphragm. Generally improved.	Fulfilled.	July 1932. General condition fairly good, and A. P. space almost obliterated. Outlook doubtful: condition of right lung not satisfactory.

TABLE II (continued)

No.	Indication.	Date.	Length of nerve.	Rise of diaph.	Result.	Indication fulfilled or not.	End. result.
32	Irregular A. P. of left lung with many adhesions and one big broad adhesion from base to diaphragm. Phrenic evulsion (1) to relax the basal adhesion, (2) to improve collapse.	26.10.31	11 cm.	5 cm.	Great shortening of basal adhesion took place; considerable improvement in degree of collapse. Phrenic evulsion did not prevent the occurrence of an effusion and did not decrease the size or frequency of refills.	Fulfilled.	She developed a secondary intestinal tuberculosis and amyloid disease of the kidneys. Died.
35	Left A. P.—collapse of upper lobe, but some adhesions. Lower lobe adherent. Phrenic evulsion to aid collapse of the lower lobe.	1.3.32	10.5 cm.	5.2 cm.	No real change: apical adhesions shortened slightly. Did not prevent the formation of a cavity in the apex of the lower lobe: did not decrease the size or frequency of refills.	Not fulfilled. Subsequent screen examinations showed that the lower lobe was not really adherent but was very well expanded. There was therefore no real indication for the operation.	Alive and well (1.10.32).
37	Left A. P. with adherent upper lobe and strong adhesion from base of lung to diaphragm causing 'tenting' of the diaphragm. Phrenic (1) to relax the basal adhesion, (2) to allow further contraction of the adherent upper lobe.	1.3.32	28 cm.	4.5 cm.	Great shortening of the basal adhesion resulted; further contraction of the adherent upper lobe. Frequency of refills reduced.	Fulfilled.	Alive and well (1.10.32).
43	Left A. P.—irregular collapse with many adhesions to upper and lower lobes. Phrenic evulsion to relax adhesions and improve collapse of the lung.	5.4.32	9.5 cm.	2.8 cm.	The degree of collapse was considerably improved. Refills then became small and difficult to give and the diaphragmatic paralysis appeared to hasten the onset of pleural symphysis.	(1) Immediate indication fulfilled, (2) disadvantageous in that it hastened pleural symphysis. The diaphragm paralysis may be of value if complete obliteration of A. P. takes place.	31.7.32. Generally fairly well: small effusion and lower half of lung almost completely expanded. Thoracoplasty may be necessary.
50	Left A. P.—good collapse; pleural thickening and signs of pleural symphysis set in.	25.7.32	16 cm.	3.5 cm.	Complete expansion of the lung and obliteration of the A. P. took place.	Fulfilled.	28.1.33. Generally very well.

Left A. P.—good collapse; pleural thickening and signs of pleural symphysis set in. Onset of effusion hastened symphysis, with progressive expansion of upper lobe and of lower lobe below fluid. Adhesion from pericardium at apex of heart to diaphragm. Phrenic evulsion (1) to reduce the size of the hemithorax and give the maximum of collapse when complete expansion took place, (2) to relax the pericardial adhesion.

25.7.32 16 cm. 3.5 cm.

Complete expansion of the lung and obliteration of the A.P. took place. No fresh signs of activity and he remained very well. Heart, which was previously pulled to left, returned to its normal position.

28.1.33. Generally very well.

TABLE III. *Phrenic Evulsion as Sole Operative Procedure*

(a) *Predominantly Lower Lobe Lesion.*

No.	Indication.	Date of evulsion.	Length of nerve.	Rise of diaph.	Result.	Indication fulfilled or not.	End. result.
1	Extensive disease of right lung, with big upper lobe cavity. Dense active disease of left lower lobe. Sputum copious. Temperature high. Phrenic evulsion an attempt to control disease of left lower lobe and give symptomatic improvement.	17.8.26 Left	10 cm.	5 cm.	No evidence of clinical improvement: she steadily got worse.	Not fulfilled.	Died.
2	Massive active disease of right lower lobe: lighter active infiltration of lung above and some perihilar disease of left lung. Signs of intestinal tuberculosis and A. P. therefore not attempted. Phrenic evulsion, an attempt to control disease of right lower lobe.	17.8.26	5 cm.	5.5 cm.	Symptomatic improvement. Definite degree of healing in right lower lobe occurred and she improved temporarily. Symptoms recurred and A. P. induced: partial and abandoned. Active spread to left followed, and she steadily got worse.	Fulfilled in so far as she improved symptomatically and the disease in the right lower lobe definitely improved. Not effective in checking the progressive nature of her illness.	Developed secondary intestinal tuberculosis and died.

TABLE III (continued)

No.	Indication.	Date of evulsion.	Length of nerve.	Rise of diaph.	Result.	Indication fulfilled or not.	End. result.
4	Exudative tuberculosis of left lower lobe: fairly extensive involvement of right lung. General condition bad. Phrenic evulsion done in an attempt to control disease of left lower lobe.	27.5.29	9 cm.	4.8 cm.	Despite great condensation of the disease in the left lower lobe there was no real improvement. The disease slowly progressed and intestinal tuberculosis developed.	Not fulfilled.	Died.
16	Dense fibrocaceous disease of right lower lobe; upper half of right lung and left lung healthy. Phrenic evulsion to collapse and rest the right lower lobe.	27.4.31	2 cm.	2 cm.	Improved for a time but did not prevent a cavity forming in the right lower lobe and a spread to the left lung ultimately took place.	Not fulfilled.	Died.
30	Fibrotic disease of right lung with medium-sized cavity in the lower lobe. Phrenic evulsion, an attempt to close the lower lobe cavity.	20.10.31	35 cm.	6.5 cm.	Result excellent. Great reduction in size of cavity in lower lobe—reduced to a small slit.	Fulfilled.	Active and well (31.7.32).
39	Dense disease of right lower lobe with a huge cavity with a fluid level. Light infiltration of lung above and of the left lung. Phrenic evulsion to control the disease of the right lower lobe and to collapse the cavity.	9.3.32	16 cm.	5.6 cm.	Result excellent. Basal disease completely collapsed and cavity obliterated. Disease in other parts of the lungs improved simultaneously.	Fulfilled.	Active and well (1.10.32).
42	Infiltration of both lower lobes, most marked in the left. Phrenic evulsion to control the disease in the left lower lobe.	23.4.32	4 cm.	No rise.	Diaphragmatic paralysis was only partial and temporary and had no effect on the condition.	Not fulfilled.	31.7.32. Condition unchanged.

(b) Cases with Predominantly Upper Lobe Lesions.

18	Contracting fibroid disease	18.6.31	11 cm.	7.6 cm.	Result excellent. The right upper lobe became	Fulfilled.	Active	Spread to left lung controlled by A.P. 3.6.32.
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(b) *Cases with Predominantly Upper Lobe Lesions.*

- |    |   |         |        |                                |   |  |  |
|----|---|---------|--------|--------------------------------|---|--|--|
| 18 | Contracting fibroid disease of right upper lobe, containing cavities. Perihilar fibrotic disease of left lung. General condition very good. Phrenic evulsion, done to allow further contraction of the upper lobe and if possible closure of the cavities.  | 18.6.31 | 11 cm. | 7.6 cm.                        | Result excellent. The right upper lobe became progressively smaller and fibroid and cavities were much reduced in size but did not quite close.   | Fulfilled. Active signs appeared in left lung 4 months later. Infiltration of an inactive nature had been present since admission in the left lung and the phrenic evulsion could not be held responsible for the recrudescence. | Spread to left lung controlled by A.P. 3.6.32. 1.10.32. Improving and general condition good.  |
| 21 | Contracting fibroid right upper lobe containing five fair-sized cavities. Lung below and left lung healthy. Phrenic evulsion done to allow further contraction of the right upper lobe and if possible closure of the cavities.   | 25.6.31 | 10 cm. | 4.6 cm.                        | Result very good. The right upper lobe became further contracted and densely fibroid; the cavities did not quite close.   | Fulfilled.   | She remained very well for many months, but when last heard of (31.7.32) she was in bed with advanced bilateral active tuberculosis. |
| 22 | Fibrotic disease of right upper lobe with a cluster of small cavities near the apex. Zone of infiltration in centre of lung and active area of disease in centre of left lung. Phrenic evulsion to allow further contraction of the right upper lobe.   | 30.6.31 | 5 cm.  | 5.8 cm.                        | Disease of right upper lobe became of a diffuse fibrotic nature and the cavities became smaller. Central zone of infiltration in right lung and active area in left largely cleared. Result good. | Fulfilled.   | Developed intestinal tuberculosis and went down hill. 21.7.32. General condition bad and outlook poor. Died later.                   |
| 23 | Dense disease, becoming fibroid, of right upper lobe, containing cavities. Dense disease of right base (still active), and light infiltration of the intervening lung. Light infiltration spread from root into left upper lobe. Phrenic evulsion to allow further contraction of right upper lobe and to rest the basal disease. | 30.6.31 | 8 cm.  | 6.3 cm. (10.2 cm. above left). | Result very good. Further contraction of upper lobe took place and basal disease cleared up. She later had signs of activity in the left lung, but this settled down.                             | Fulfilled.   | 30.7.32. Right upper lobe now densely fibroid. Able to get about and feels well. Generally greatly improved.                         |

TABLE III (continued)

No.	Indication.	Date of evulsion.	Length of nerve.	Rise of diaph.	Result.	Indication fulfilled or not.	End. result.
24	Diffuse finely nodular disease of right lung, inactive; huge cavity with dense fibrous walls in left upper lobe. Phrenic evulsion (1) to ease a harassing morning cough, which occasionally led to vomiting, (2) to help to reduce the size of the upper lobe cavity—not expected to close it.	7.7.31	18 cm.	7 cm.	(1) Cough less and more productive; it caused no strain after the operation and sickness ceased, (2) cavity slightly reduced in size. A good result.	Fulfilled.	31.7.02. Generally very well but dyspnoeic on exertion.
25	Extensive disease of upper two-thirds of right lung with a large thick-walled upper lobe cavity. Disease chronic. Fibrosis of left lung generally. Phrenic evulsion to (1) to ease a very distressing cough; the effort to get up his sputum (copious) very frequently caused vomiting, (2) to aid further shrinkage of the right upper lobe.	14.7.32	15.5 cm.	4 cm.	(1) Satisfactory shrinkage of the right upper lobe and contraction of the cavity resulted, (2) cough became less, expectoration easy and sickness ceased. A good result.	Fulfilled.	This man later left the Sanatorium against advice. Admitted to poor-house very ill—the result of alcoholic excesses. While there he fell out of a window and was killed.
38	Diffuse infiltration of upper half of left lung, with a dense patch under the clavicle and many tiny cavities above. Fibrotic change in evidence. Fresh signs of activity developed in left side and after A. P. failed phrenic evulsion was done in attempt to control the disease.	9.3.32	14 cm.	4.1 cm.	She derived some temporary benefit only: symptomatic. The disease continued to be active and was in no way controlled by the diaphragmatic paralysis.	Not fulfilled.	Removed home 7.7.32 with advanced bilateral tuberculosis (active) and secondary intestinal tuberculosis. Died shortly after this.

Active and well (31.7.32).

Fulfilled.

Result very good. Disease of left upper lobe became densely fibrotic and great dim-

4.4 cm.

8.5 cm.

9.3.32

Extensive disease of upper two-thirds of left lung, becoming fibrotic, with many tiny cavities. The upper

40

40	Extensive disease of upper two-thirds of left lung, becoming fibrotic, with many small cavities in the upper half and one large cavity behind first interspace and second rib. Phrenic evulsion to allow further contraction in a lung already contracting (diaphragm already pulled up) and to aid in collapse of the cavities.	9.3.32	8.5 cm.	4.4 cm.	Result very good. Disease of left upper lobe became densely fibrotic and great diminution in the size of the cavities resulted.	Fulfilled.	Active and well (31.7.32).
41	Dense disease of right upper lobe, becoming fibrotic with a fair-sized cavity under the clavicle. Coarse nodular infiltration of left lung. Phrenic evulsion to allow of further contraction of the right upper lobe and of the cavity.	22.3.32	25.5 cm.	3.5 cm.	Satisfactory contraction of right upper lobe and reduction in the size of the cavity resulted. He was greatly improved.	Fulfilled.	6.7.32. Left sanatorium against advice. He was then very well.
45	Densely fibroid right upper lobe (contracting), with a large cavity. Right diaphragm raised. Dense disease of upper half of left lung with several fair-sized cavities. Phrenic evulsion (1) to allow further contraction of a fibrosing right upper lobe, (2) to ease a troublesome cough and difficult expectoration which frequently caused vomiting.	2.5.32	17.25 cm.	5 cm.	(1) Considerable shrinkage of right upper lobe and contraction of the cavity followed, (2) cough much less and more productive: expectoration easier and sickness ceased. Generally much improved.	Fulfilled in both instances.	31.7.32. Still in bed but improving.
48	Dense disease of right upper lobe with a large cavity below and behind the clavicle: disease becoming fibroid and upper lobe contracting. Phrenic evulsion to allow further contraction of right upper lobe and if possible closure of the cavity.	21.7.31	26.5 cm.	3.9 cm.	Marked contraction of the upper lobe resulted: it became densely fibroid with marked reduction in the size of the cavity. Temperature fell to normal and symptoms improved at the same time. An excellent result.	Fulfilled.	28.1.33. Much improved.

TABLE III (continued)  
(c) Cases of more Extensive Bi-lateral Fibrotic or Fibroid Disease

No.	Indication.	Date of evulsion.	Length of nerve.	Rise of diaph.	Result.	Indication fulfilled or not.	End. result.
6	Densely fibroid disease of the whole of the left lung with cavities at the extreme upper and lower areas. Lighter fibrotic, inactive disease of right lung. He was going home and phrenic evulsion was done (1) to aid the more extensively diseased lung, and (2) to ease a very troublesome cough.	3.6.29	24 cm.	4.6 cm.	Increased density of the shadows (as seen on X-ray) in lower two-thirds of left lung and marked reduction in the size of the cavities took place. Cough became loose and easy and he was better in every way.	Fulfilled.	He was discharged feeling very well, but two months later he dropped down dead—cause unknown.
11	Dense fibroid disease of the whole of the right lung with three large cavities in the upper lobe. Generalized fibrosis of left with dense mass at the base becoming fibrotic. There was a very marked scoliosis with the convexity to the left and the trachea was greatly displaced to the right. Thoracoplasty would be difficult and A. P. impossible. Phrenic evulsion (1) to allow as much reduction in volume of left lung as possible and to prevent an increase in the scoliosis, (2) to ease a troublesome cough.	18.8.30	11 cm.	?	She improved for a time and cough was easier. No change in the scoliosis occurred and it had no effect on restoring the trachea to position—(it was much displaced to the right). Her condition slowly deteriorated and an active spread to the left lung took place.	Doubtfully fulfilled. It was not to be expected that a phrenic evulsion as an isolated procedure would greatly influence the course of the disease.	Died 6.3.32.
27	Dense disease of the upper half of the left lung, still	8.9.31	12 cm.	5.5 cm.	There was very little immediate change. Improvement was slow	Fulfilled.	31.7.32. Generally very well.

27	Dense disease of the upper half of the left lung, still active but becoming fibrotic; several cavities lying under the clavicle. Diffuse fibrotic disease of the right lung. He was not improving; attempt at left A. P. failed. Phrenic evulsion (1) to give as great a degree of collapse as possible to a lung already showing signs of contracting, (2) to ease a very troublesome cough.	8.9.31	12 cm.	5.5 cm.	There was very little immediate change. Improvement was slow but steady. Nine months later he was greatly improved: disease in the left upper lobe had become dense and fibroid. Cough became very much easier. A late excellent result.	Fulfilled.	31.7.32. Generally very well.
31	Left lung completely diseased; chronic localized pyopneumothorax with broncho-pleural fistula. Pleura everywhere greatly thickened and with calcified plaques. Cough severe, sputum copious and he was not improving. Thoracoplasty contra-indicated and A. P. impossible. Phrenic evulsion to give as much benefit as possible.	20.10.31	4 cm.	2 cm.	He afterwards, if anything, emptied the pyopneumothorax more easily. Operation had no effect on reducing the amount of sputum and there was no change in the lung condition.	Not fulfilled: no real indication.	31.7.32. Generally much better and able to get about, but dyspnoeic. Possibly nothing to do with his phrenic evulsion. Difficult to assess.
36	Dense disease of upper two-thirds of left lung with commencing fibrotic change, and with one large and several small cavities below the clavicle. Infiltration, showing commencing healing of upper and mid zones of right lung. Phrenic evulsion to allow further collapse and contraction in a lung already contracting (shown by left diaphragm being already pulled up).	1.3.32	15 cm.	3.4 cm. (left diaph. 4.5 cm. above right.)	The cavities in the upper lobe were greatly reduced in size, and there was considerable clearing of the disease shadowing as seen on X-ray. Marked general improvement; late result excellent.	Fulfilled.	31.7.32. Active and very well.

TABLE III (continued)

No.	Indication.	Date of evulsion.	Length of nerve.	Rise of diaph.	Result.	Indication fulfilled or not.	End. result.
49	Extensive disease of upper two-thirds of right lung, dense and appearing still active, with irregular cavitation in the upper lobe. Fibrotic change commencing; diaphragm raised. Light fibrotic disease of mid zone of left lung, with cavitation. Phrenic evulsion to allow of further collapse and contraction in a lung already fibrosing.	25.7.32	24 cm.	4.4 cm.	Further contraction of the left upper lobe and reduction in the size of the cavities took place; marked clearing of disease shadowing of lung below. Slow but steady improvement in his general condition and the symptoms took place. Late result excellent.	Fulfilled.	28.1.33. Active and very well.

TABLE IV. Cases in which the Main Indication was for Relief of Symptoms

No.	Indication.	Date.	Length of nerve.	Rise of diaph.	Result.	Indication fulfilled or not.	Remarks.
8	A. P. followed by effusion—obliteration of A. P. and lung became fibroid. Persistent pain over left lower ribs, in neck and shoulder passing down the left arm; associated with twitching of shoulder muscles. Phrenic evulsion primarily to relieve pain.	16.1.30	1 cm.	4 cm.	Pain entirely ceased: three weeks later there was a slight return of the pain experienced over the left costal margin.	Fulfilled.	Thoracoplasty done. Included in section on 'Thoracoplasty'.
9	Fibrotic disease of left lung. She had persistent pain over the lower part of the left lung, passing up to the shoulder. Phrenic evulsion primarily for relief of pain.	30.1.30	14 cm.	5.5 cm.	Pain quite ceased.	Fulfilled.	Thoracoplasty ultimately done. Included under 'Thoracoplasty'.

20	Dense disease of left upper	25.6.31	9 cm.	?	Cough less and more productive: sputum decreased.	Fulfilled.	Discharged July, 1932: lung condition then
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20	Dense disease of left upper lobe with a huge cavity: dense largely calcified disease of lung below. Right lung healthy. Generally well and thoracoplasty not necessary. Cough very troublesome and phrenic evulsion done to ease emptying of a chronic cavity. She had severe rheumatoid arthritis.	25.6.31	9 cm.	?	Cough less and more productive: sputum decreased in amount and she became really very well.	Fulfilled.	Discharged July, 1932: lung condition then quiescent: cough slight.
24	Huge dense walled cavity in left upper lobe. Phrenic evulsion (1) to ease a harassing morning cough which frequently caused a feeling of sickness and occasionally vomiting, (2) to reduce size of upper lobe cavity.	7.7.31	18 cm.	7 cm.	(1) Cough much less after operation and caused much less strain. Cavity emptied more easily and the feeling of sickness and vomiting ceased, (2) slight reduction in size of cavity.	Fulfilled.	Case included under 'upper lobe lesions': 31.7.32. Active and well.
25	Extensive chronic disease of upper two-thirds of right lung with large, thick-walled upper lobe cavity. Phrenic evulsion done chiefly to aid cough and expectoration. Sputum was copious (4 oz.) and expectoration very difficult, frequently causing vomiting.	14.7.31	15.5 cm.	4 cm.	Cough less and expectoration easier: sickness ceased. Sputum gradually fell to $\frac{1}{4}$ oz. daily and he was very much better.	Fulfilled.	Case included under 'upper lobe lesions'.
26	Dense disease of right upper lobe with a big cavity: infiltration, becoming fibrotic, of lung below and fibrotic disease of left lung. Phrenic evulsion primarily done to ease a very harassing morning cough. Thoracoplasty was in view.	8.9.31	2 cm.	?	Sputum at first increased and then fell to usual amount but looser and more easily voided. Phrenic evulsion did not prevent signs of activity developing later in this lung.	Immediate indication fulfilled.	Thoracoplasty refused. She settled down and on discharge, June, 1932, was much better: outlook not good.

TABLE IV (continued)

No.	Indication.	Date.	Length of nerve.	Rise of diaph.	Result.	Indication fulfilled or not.	Remarks.
27	Extensive bilateral disease becoming fibrotic and more dense in the left, where there were upper lobe cavities. Phrenic evulsion to ease a very harassing cough and to give as much collapse as possible to the left lung, which was fibrosing.	8.9.31	12 cm.	5.5 cm.	Cough became much easier after operation and he felt much better. There was a slow steady improvement in the lung condition.	Fulfilled.	Included under section 'more extensive fibrotic lesions'.
34	Dense active disease of whole of left lung with a huge upper lobe cavity. Severe haemoptysis before admission and several large haemoptyses on 5.2.32. Extremely ill. Left A. P. failed. Phrenic evulsion (1) in attempt to control haemoptysis, (2) thoracoplasty in view.	5.2.32	10 cm.	?	Phrenic evulsion had no effect in controlling the haemorrhage. The disease extended and she got steadily worse and died.	Not fulfilled.	Included under section on 'Thoracoplasty'.
45	Extensive bilateral tuberculosis: right upper lobe fibroid, and containing a large cavity. Phrenic evulsion primarily to ease cough and expectoration: the effort to get up his sputum frequently caused vomiting.	2.5.32	17.25 cm.	5 cm.	Cough became less: sputum was more easily voided and vomiting ceased. He was very much more comfortable.	Fulfilled.	Included under 'upper lobe lesions'.
46	Dense fibroid disease of whole of left lung with a huge upper lobe cavity. Fairly dense, still active disease of right upper lobe. Phrenic evulsion done to ease a very troublesome cough: she had great difficulty in getting up her sputum.	23.5.32	34 cm.	4.6 cm.	Temperature fell and became steady after operation; sputum at first increased and then decreased: cough was less, sputum more easily voided and she was generally much better.	Fulfilled.	There was no real change in her condition beyond a symptomatic benefit. Temperature again became irregular and the amount of sputum came back to its previous level but expectoration remained easy.

The phrenic evulsion

Fulfilled.

Result excellent. Tem-

5.6 cm.

36 cm

14.6.32

Dense active disease of whole of left lung with a huge upper lobe cavity. Fairly dense, still active disease of right upper lobe. Phrenic evulsion done to ease a very troublesome cough: she had great difficulty in getting up her sputum.

47	Dense fibrocascous condition of whole of left lung with several large cavities in the upper lobe. Right upper lobe fibroid. Phrenic evulsion to ease a cough which was constant and harassing: the cough induced vomiting, sometimes as often as four times a day. Sleep was much disturbed.	14.6.32	36 cm. (47 with filament)	5-6 cm.	Result excellent. Temperature fell and became steady; cough was much less, sickness ceased and sleep now became possible. Amount of sputum decreased to 2 oz., there was a marked general improvement.	Fulfilled.	The phrenic evulsion was not expected to influence the lung condition noticeably, but a big rise of the diaphragm occurred and there was undoubted diminution in the size of the upper lobe cavities.
51	Right upper lobe completely excavated: infiltration of lung below and of mid-zone of left. 6.8.31. Haemoptysis of 6 oz. and she continued to bring up small quantities of blood for next two days. Phrenic evulsion attempted to control the bleeding	8.8.32	—	—	The bleeding stopped more or less at once and there was no recurrence.	Fulfilled.	Considerable relaxation of the right upper lobe occurred as shown by the cavity assuming an ovoid shape with the long axis lying transversely.

Table Showing Effect of Phrenic Evulsion on Symptoms

Date of operation.	Side.	Cough.		Expectoration.		Amount of sputum.		T. B. in sputum.		Temperature.		Remarks.
		Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.	
3 9.1.29	Lt.	Severe	Less	Difficult	Easier	5½ oz.		Pos.	Pos.	102.6°F.	Slight fall	Thoracoplasty 24.1.29
5 27.5.29	Lt.	Not trouble-some	No change	Easy	No change	Fraction	No change	Pos.	Pos.	99.5°F.	No change	Thoracoplasty
7 27.5.29	Lt.	Severe	Less	Difficult	Easier	2 oz.	Decrease	Pos.	Neg. (after Th.)	101°F.	Fall	Improved after phrenic Thoracoplasty 24.6.30
8 16.1.30	Lt.	Nil	No change	Nil	No change	Nil	No change	No sputum		99.2°F.	Fall	Thoracoplasty 13.2.30
9 30.1.30	Lt.	Trouble-some	No change	Difficult	No change	1½ oz.	No change	Pos.	Neg. (after Th.)	101°F.	No change	Thoracoplasty 7.5.30
10 5.6.30	Rt.	Trouble-some	No change	Difficult	No change	2½ oz.	No change	Pos.	....	100.6°F.	No change	Thoracoplasty 16.6.30
12 25.8.30	Lt.	Not severe	Worse	Mod. easy	No change	½ oz.	Increased	Pos.	Pos.	99°F.	No change	Thoracoplasty 13.11.30
13 3.11.30	Lt.	Trouble-some	Less	Difficult	Easier	1 oz.	Increased	Pos.	Pos.	102°F.	No change	Improved Thoracoplasty 4.12.30
17 7.5.31	Lt.	Not severe	No change	Mod. easy	No change	1 oz.	No change	Pos.	Neg. (after Th.)	102°F.	No change	Thoracoplasty 25.5.31
28 13.8.31	Lt.	Slight	Less	Easy	No sputum	Fraction	Decrease	Pos.	No sputum	101°F.	Fall	—
33 1.12.31	Rt.	Trouble-some	No change	Difficult	Easier	½ oz.	Increase at first then decrease	Pos.	Pos.	100.4°F.	Fall	—
34 5.2.32	Lt.	Severe	No change	Difficult	No change	3 oz.	No change	Pos.	Pos.	101°F.	Increase	—

44 25.4.32 Rt. Trouble-some No Difficult No 1½ oz. No Pos. Normal No

44	25.4.32	Rt.	Trouble- some	No change	Difficult	No change	1½ oz.	No change	Pos.	Pos.	Normal	No change	—
14	22.12.30	Lt.	Not severe	Less	Difficult	Easier	1 oz.	Increase at first then de- crease	Pos.	Neg.	100°F.	Fall	A.P.-effusion
15	5.1.31	Lt.	Severe	No change	Difficult	No change	2½ oz.	Increase	Pos.	Pos.	101°F.	Increase	—
19	18.6.31	Lt.	Slight	No change	Mod. easy	Easier	Fraction	No change	Neg.	Neg.	Normal	No change	A.P.-effusion
29	5.10.31	Lt.	Trouble- some	Less	Mod. easy	No change	1½ oz.	No change	Pos.	Pos.	99-6°F.	No change	A.P.-effusion
32	26.10.31 <sup>s</sup>	Lt.	Severe	Much less	Difficult	Easier	1 oz.	Decrease tem- porary	Pos.	Pos.	Normal	No change	A.P.
35	1.3.32	Lt.	Not trouble- some	No change	Mod. easy	No change	¾ oz.	No change	Pos.	Pos.	99°F.	No change	A.P.
37	1.3.32	Lt.	Not trouble- some	No change	Mod. easy	Easier	¾ oz.	Increase at first then de- crease	Pos.	Pos.	Normal	—	A.P.
43	5.4.32	Lt.	Not trouble- some	No change	Mod. easy	No change	¾ oz.	Increase	Pos.	Pos.	100°F.	Fall, fol- lowed by a rise	A.P.
50	25.7.32	Lt.	Not trouble- some	No change	Mod. easy	Easier	¾ oz.	Decrease	Neg.	Neg.	99°F.	No change	A.P.
1	17.8.26	Lt.	Trouble- some	No change	Difficult	No change	3 oz.	No change	Pos.	Pos.	102-8°F.	Increase	—
2	17.8.26	Rt.	Trouble- some	Less	Difficult	Easier	15 oz.	Decrease	Pos.	Pos.	103°F.	Fall	—
4	27.5.29	Lt.	Trouble- some	No change	Difficult	No change	2 oz.	Increase	Pos.	Pos.	101-2°F.	Increase	—
16	27.4.31	Rt.	Trouble- some	Less	Difficult	Easier	1 oz.	Temp. decrease	Pos.	Pos.	101°F.	Fall, then rise	—
30	30.10.31	Rt.	Not trouble- some	No change	Easy	No change	1 oz.	Decrease	Pos.	Pos.	Normal	No change	—

Table Showing Effect of Phrenic Evulsion on Symptoms (continued)

Date of operation.	Side.	Cough.		Expectoration.		Amount of sputum.		T. B. in sputum.		Temperature.		Remarks.
		Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.	
39 9.3.32	Rt. Trouble-some	Less		Difficult	Much easier	3 oz.	Increase at first then steady decrease	Pos.	Pos.	101-4°F.	Fall	—
42 5.4.32	Lt. Trouble-some	No change		Difficult	No change	2 oz.	No change	Pos.	Pos.	99-4°F.	No change	Paralysis temporary
18 18.6.31	Rt. None	No change		None	No change	No sputum	—	Neg.	Neg.	Normal	No change	—
21 25.6.31	Rt. Not trouble-some	No change		Easy	No change	Fraction	No change	Pos.	Pos.	Normal	No change	—
22 30.6.31	Rt. Severe	Much less		Difficult	Easier	3 oz.	Decrease	Neg.	Pos.	102°F.	Fall and then rise	—
23 30.6.31	Rt. Severe	Much less		Difficult	Easier	3 oz.	Decrease	Pos.	Pos.	99-4°F.	No change	—
24 7.7.31	Lt. Severe	Much less		Difficult	Much easier	1 oz.	Decrease	Pos.	Pos.	Normal	No change	Operation, largely to relieve symptoms
25 14.7.31 *	Rt. Severe	Less		Difficult	Much easier	4 oz.	Decrease	Pos.	Pos.	Normal	No change	Operation, largely to relieve symptoms
38 9.3.32	Lt. Trouble-some	Temp. improved		Difficult	Temp. improved	1 oz.	Decrease followed by increase	Pos.	Pos.	102°F.	Fall, then rise	—
40 9.3.32	Lt. Slight	No change		Easy	No change	3 oz.	Increase then decrease	Pos.	Pos.	Normal	No change	—
41 22.3.32	Rt. Trouble-some	Less		Difficult	Much easier	2 oz.	Decrease	Pos.	Neg.	100-6°F.	Fall	—

45 2.5.32 Rt. Severe Much less Difficult Much 2 1/2 oz. No Pos. 100-2°F. No Operation, largely to relieve symptoms

45	2.5.32	Rt.	Severe	Much less	Difficult	Much easier	2½ oz.	No change	Pos.	Pos.	100-2°F.	No change	Operation, largely to relieve symptoms
48	21.7.32	Rt.	Trouble-some	Less	Mod. easy	Easier	2 oz.	Increase then steady fall	Pos.	Pos.	100°F.	Fall	—
6	3.6.29	Lt.	Trouble-some	Much less	Difficult	Much easier	1½ oz.	—	Pos.	...	Normal	No change	—
11	18.8.30	Rt.	Trouble-some	Sl. less	Difficult	Temp. improved	¾ oz.	Increase then decrease	Pos.	Pos.	99-6°F.	Fall	Operation, largely to relieve symptoms
27	3.9.31	Lt.	Severe	Much less	Difficult	Much easier	¾ oz.	Increase then decrease	Pos.	Pos.	100-2°F.	Fall	Relief of symptoms was one indication
31	20.10.31	Lt.	Severe	No change	Difficult	No change	5 oz.	No change	Pos.	Pos.	100-4°F.	No change	—
36	1.3.32	Lt.	Sl. trouble-some	Less	Sl. difficult	Easier	½ oz.	Increase then decrease	Pos.	Neg.	Normal	No change	—
49	25.7.32	Rt.	Not trouble-some	Less	Mod. easy	No change	¾ oz.	Increase then decrease	Pos.	Pos.	Normal	No change	—
20	25.6.31	Lt.	Trouble-some	Less	Difficult	Easier	½ oz.	Decrease	Neg.	Neg.	99-8°F.	Fall	Indication—relief of symptoms
26	8.9.31	Rt.	Severe	Less	Difficult	Easier	½ oz.	Increase then decrease	Pos.	Pos.	99-8°F.	Fall	Indication—relief of symptoms
46	23.5.32	Lt.	Trouble-some	Less	Difficult	Easier	1 oz.	Increase then decrease	Pos.	Pos.	100-2°F.	Fall, then rise	Indication—relief of symptoms
47	14.6.32	Lt.	Very severe	Much less	Very difficult	Easier	3 oz.	Decrease then increase	Pos.	Pos.	101-6°F.	Fall	Indication—relief of symptoms

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#### DESCRIPTION OF PLATES

PLATE 4, FIG. 1. Case 19. Expansion of lung under a chronic effusion: the lung is creeping out on the paralysed diaphragm.

FIG. 2. Same case—after removal of effusion.

FIG. 3. Case 39: 24.2.32. Extensive infiltration of right lower lobe with a huge cavity with a fluid level. Light infiltration of left lung. Right diaphragm raised. Phrenic evulsion 9.3.32.

FIG. 4. Case 39: 13.4.32. Big rise of diaphragm with complete collapse of the basal disease and obliteration of the cavity.

FIG. 5. Case 32: 16.6.31. Extensive disease of left lung with three large cavities in upper half. A.P. induced 18.6.31.

FIG. 6. Case 32: 24.10.31. Irregular left A.P. with many adhesions and one big broad adhesion from base to diaphragm. Phrenic evulsion 26.10.31.

PLATE 5, FIG. 7. Case 32: 3.11.31. Collapse of lung much improved: great shortening of the basal adhesion: diaphragm raised to ninth interspace.

FIG. 8. Case 32: 17.11.31. Left anterior oblique radiogram, showing good anterior collapse. The raised diaphragm is seen as a thin curved line.

FIG. 9. Case 30: 16.12.30. Extensive disease shadowing of the right lung, dense in the lower half; generalized fibrosis of the left lung.

FIG. 10. Case 30: 24.6.31. A marked improvement has taken place: disease now fibrotic but a fair-sized cavity has formed in the lower lobe.

FIG. 11. Case 30: 8.10.31. Appearance generally the same as in 10; but the cavity has increased in size. Phrenic evulsion 20.10.31.

FIG. 12. Case 30: 6.1.32. The cavity has been reduced to a small slit lying below the inner end of the eighth rib. Diaphragm high. (The large ring at the base is pleural.)

PLATE 6, FIG. 13. Case 18: 31.12.30. Dense disease of right upper lobe with thickened interlobar septum. Light disease of lung below and perihilar shadowing on left.

FIG. 14. Case 18: 5.3.31. The upper lobe is contracting and contains several cavities. Lung below clearer.

FIG. 15. Case 18: 16.6.31. Right upper lobe further contracted and fibroid. Cavities contracting trachea and heart pulled to right. Phrenic evulsion 18.6.31.

FIG. 16. Case 18: 20.4.22. Diaphragm high-marked further contraction of right upper lobe. Cavities still visible. Heart in better position.

PLATE 7, FIG. 17. Case 18: 1.6.32. Right side unchanged. Big infiltration into mid-zone of left lung with a central cavity. Left A.P. 3.6.32.

FIG. 18. Case 18: 22.6.32. Showing right diaphragmatic paralysis with left A.P. induced to control the spread to that side.

FIG. 19. Case 40: 17.11.31. Central infiltration on right. Infiltration becoming fibrotic of upper two-thirds left lung with many small cavities and one large cavity with fluid level, opposite first interspace and second rib.

FIG. 20. Case 40: 24.2.32. Definition of shadows improved—many small cavities. The big cavity is now thicker walled and has increased slightly in size. Diaphragm pulled up. Phrenic evulsion 9.3.32.

FIG. 21. Case 40: 13.6.32. Diaphragm well raised. Disease in left upper lobe now fibrotic. The big cavity is already greatly reduced in size—now a narrow slit lying in scar-tissue above the second costal cartilage.

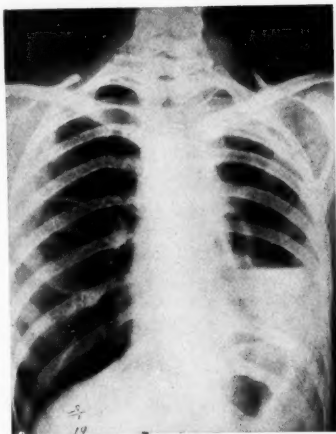


FIG. 1



FIG. 2

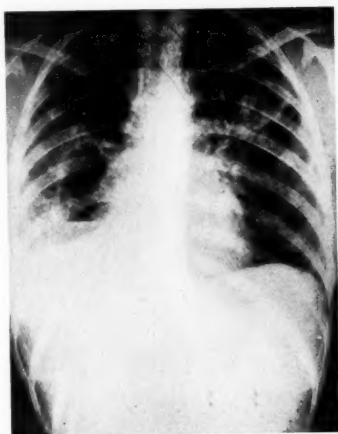


FIG. 3



FIG. 4

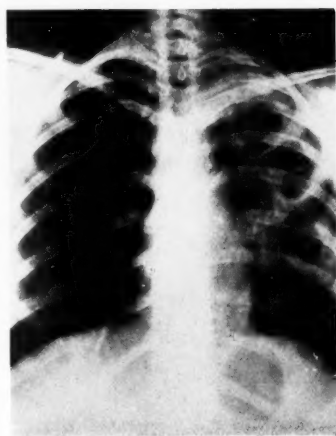


FIG. 5

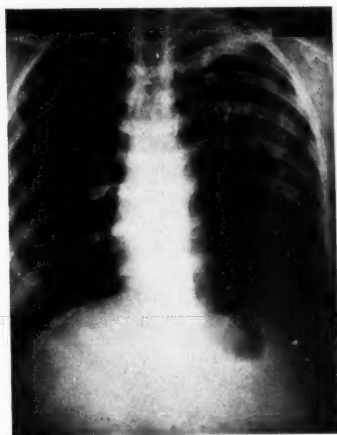


FIG. 6



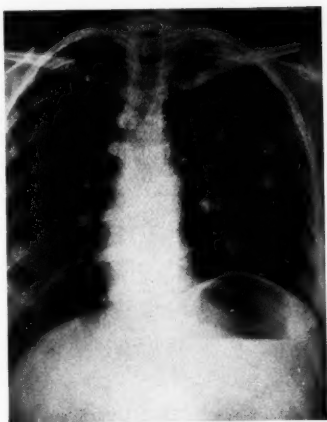


FIG. 7

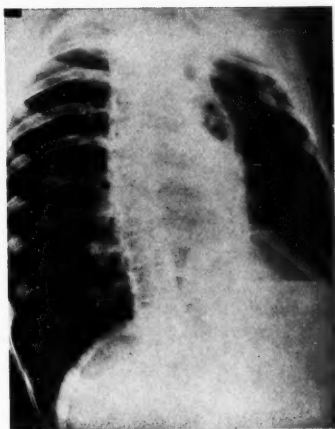


FIG. 8

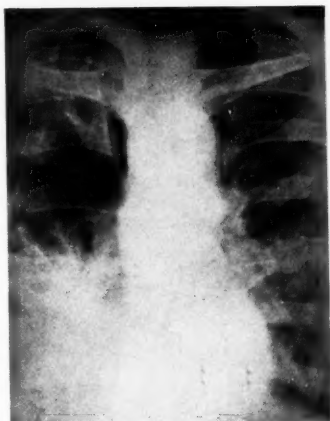


FIG. 9

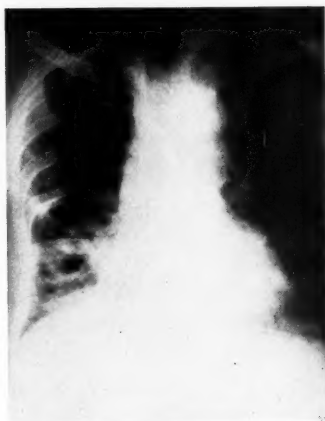


FIG. 10

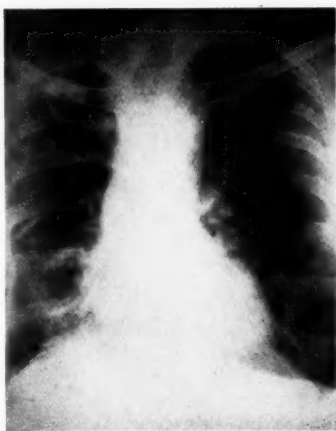


FIG. 11

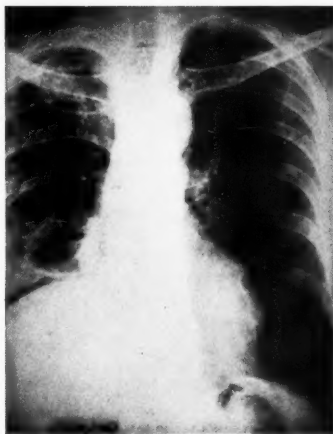


FIG. 12





FIG. 13

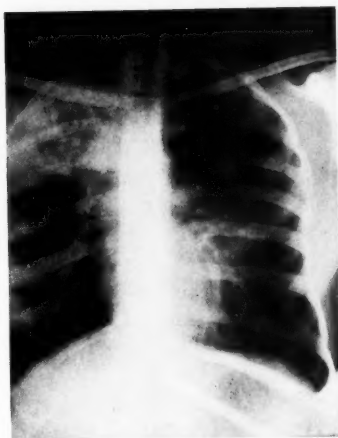


FIG. 14



FIG. 15



FIG. 16



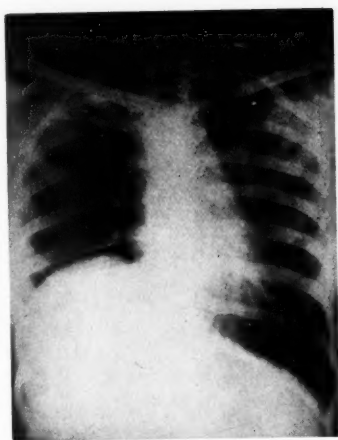


FIG. 17



FIG. 18

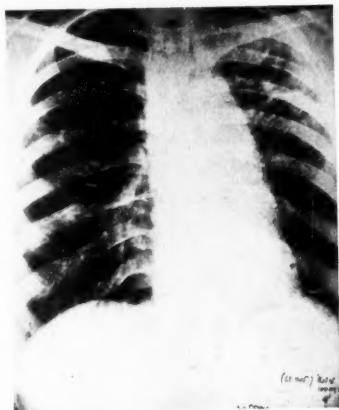


FIG. 19

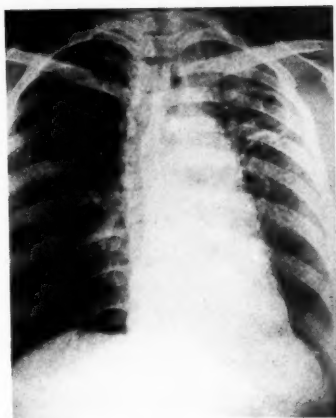


FIG. 20

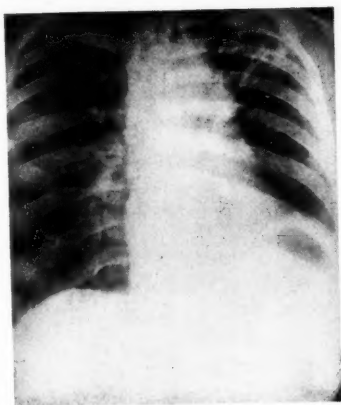
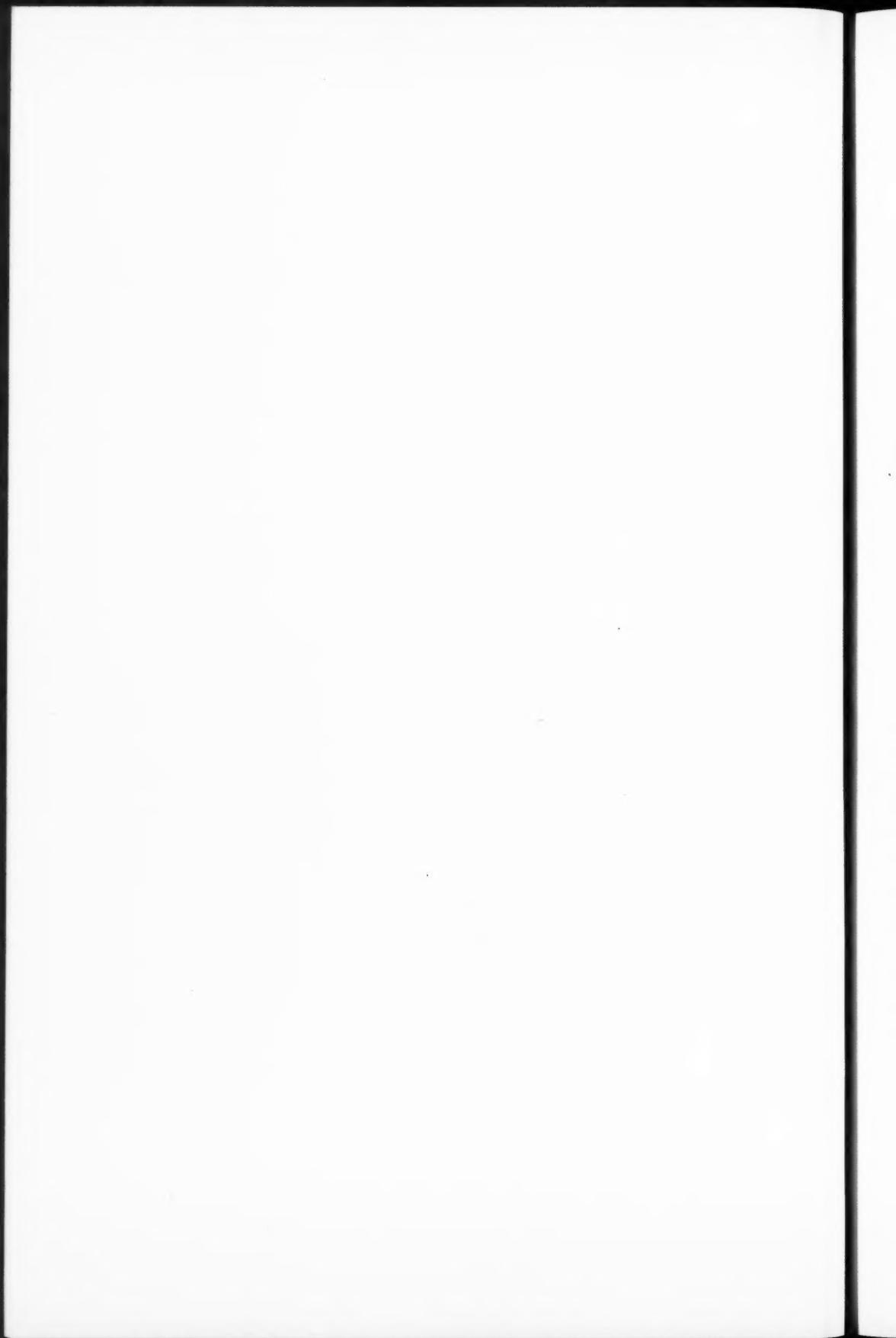


FIG. 21



## BASOPHIL ADENOMA OF THE PITUITARY GLAND<sup>1</sup>

BY JOHN CRAIG AND BRENNAN CRAN

(From the Aberdeen Royal Infirmary)

With Plate 8

REPORTED cases of basophil adenoma of the pituitary gland are uncommon, although some association between basophil adenomata and obesity with virilism in women has been observed for several years. In 1926 F. Parkes Weber gave an excellent report (1) of a case showing such an association. Finally, Cushing (2) in 1932 established the syndrome by publishing his own cases and others from the literature.

In this article, a case of basophil adenoma of the pituitary body is described, which was diagnosed during life and confirmed by autopsy.

### *Case Report.*

The patient, a female aged 28, was seen first on August 25, 1932. She was unmarried and had been in good health four years previously (Plate 8, Fig. 1). At that time she began to get stout about the abdomen and chest, and soon after the upper arms and thighs also got big. The obesity rapidly increased, and in a few months she had gained four stones in weight. Some months before the onset of the obesity, hair began to grow on her chin, and during the four years of her illness, the hair on the face and lips increased, as also did the hair on her limbs. The menstrual periods had always been regular, and normal, but from the onset of the illness they became irregular—usually coming at three-monthly intervals. They stopped altogether in April, 1932.

For two years she had occasional frontal headaches, especially in the mornings. For eighteen months increasing breathlessness was complained of, and she had several attacks of acute dyspnoea during the last few months. From the onset of the illness she had become increasingly highly coloured, and had noticed an increase in the pigmentation about her face. The fronts of her legs had been 'black and blue' from time to time, and had got gradually more and more discoloured. In the last year she had 'rheumaticky pains' in her arms and legs. The obese areas in her arms and thighs had also been painful.

Her mother died of cancer of the uterus and her father is still alive. Four sisters and three brothers are alive and well. There is no family history of obesity. She had scarlet fever and diphtheria as a girl. She never was pregnant.

<sup>1</sup> Received October 4, 1933.

*Examination.* She was a plethoric woman who weighed fifteen and a half stones, and was five feet four inches in height (Plate 8, Fig. 2). There was diffuse brown pigmentation in places on the face, which was rather obscured by her blue colour. There was a well-marked growth of hair on the chin, the upper lip, and the lower cheeks. There was some dark hair on the back of her hands and forearms, and on the shoulders and thighs. The hair of her head was dark brown in colour and plentiful. The eyes seemed slightly prominent. The upper arms and thighs were larger than normal from deposition of fat. The fat areas were in places painful on palpation. The forearms and lower legs were not increased in size. The arms generally were rather blue, the blueness being most marked about the hands and wrists. There was some brown pigmentation about the arms. There were many dark brown pigmented spots on the tibial surfaces of both legs, as well as some transverse striae and a few ecchymoses. Just over the middle thirds of the tibiae, the skin was atrophic and shiny in places. The whole appearance of the lower legs was very unusual (Plate 8, Fig. 3). There was slight oedema about the ankles. Fatty masses were also found over the lower cervical vertebrae, and fatty masses were present on each thigh continuous to the labia. The breasts were large, fatty, pendulous, and showing a bluish tinge, some dark brown pigmented spots and a few striae. The trunk generally was obese and the abdomen corpulent and protuberant. The abdomen was covered with large striae, some purple and some pale, and obviously of different dates. The hair on the abdomen had a masculine distribution. The teeth were good and not spaced. The skin was moist.

The apex beat was in the mid-clavicular line, the first sound at the mitral was rather loud, and the second sound at the aortic area was accentuated. The blood-pressure in the right arm was 180/118, and in the left arm 178/116. The spleen was not enlarged, and the liver came to the costal margin in the nipple line. No tumours could be felt in the abdomen. The lungs were normal. The urine contained a faint trace of albumin, but no proteose. The specific gravity of the urine was not fixed, and the deposit was scanty and showed an occasional pus cell and calcium oxalate crystal. The blood urea was 23 mg. per cent. The blood count showed 110 per cent. haemoglobin, 6,190,000 red cells and 7,400 white cells, of which 64 per cent. were polymorphonuclears. No abnormal cells were seen in the films.

The serum calcium was 10.8 mg. per cent., and the plasma phosphates were 2.01 mg. per cent. A sugar tolerance test was done, and the following were the blood-sugar figures after fifty grm. of glucose :

Fasting blood-sugar	.	.	.	.	.	0.092 per cent.
Half hour	.	.	.	.	.	0.104 " "
One hour	.	.	.	.	.	0.109 " "
One and a half hours	.	.	.	.	.	0.133 " "
Two hours	.	.	.	.	.	0.109 " "

Nothing abnormal was found generally in the nervous system. The optic disks were slightly pale, somewhat uniform in colour, but the colour was within physiological limits. The fields of vision were full. Visual acuity was good.

The Wassermann reaction of the blood was negative. Radiograms showed general decalcification of all the bones of the body. No cystic areas were seen in any of the bones. The skull, however, showed several small decalcified areas. The sella turcica measured 16 mm. antero-posteriorly and 10 mm. in depth.

An examination *per vaginam* was possible, and the pelvic organs were found to be normal. The urinary tracts were visualized by Uroselectan B, and the radiograms showed the pelvis and ureters to be normal in shape and position.

The case was clinically diagnosed as a basophil adenoma of the pituitary, from the history and examination; the salient points being the rapidly acquired plethoric obesity, the amenorrhoea, the hirsuties, the vascular hypertension, the polycythaemia, the marked striation of abdomen, the osteoporosis of bones, the curious pigmentation of the skin of the legs, and the acrocyanosis. Accordingly, deep X-ray therapy applied to the pituitary gland was undertaken, and exposures were given over five areas—frontal, vertical, occipital, right temporal, and left temporal. She came back for a second course in December 1932, and was then found to have a suppurative prepatellar bursitis. While in hospital she developed a common cold, which led in a few days to a purulent pneumococcal bronchitis, and she died on January 7, 1933, with a right-sided empyema.

*Post-mortem examination* (One hour after death).

*Summary of lesions.* Basophil adenoma of the anterior lobe of the pituitary gland. Obesity. Growth of coarse hair on face, trunk, and extremities, masculine in distribution. Enlargement of, and haemorrhage into, the suprarenal glands. Early 'colloid' goitre. Softening of the calvarium. Arterial sclerosis. Hypertrophy of the left ventricle. Dilatation of the heart. Venous congestion of the viscera. Empyema of the right pleural cavity, with complete collapse of the lung; partial collapse of the left lung. Congenital absence of the appendix. Atrophy of the mammary glands. Multiple vaginal cysts. Suppurative prepatellar bursitis.

The general appearance was that of a much older woman. Rigor mortis commencing. Marked post-mortem lividity. Lips and face deeply cyanosed. Pupils widely dilated and equal. Slight oedema of lower extremities. Brownish pigmentation of skin on anterior aspect of legs over tibiae. Extreme obesity with special deposition of fat in supraclavicular fossae, on back of neck, over abdomen and suprapubic region, and over inner part of Scarpa's triangles in the thighs. There was a profuse growth of coarse black hair which was of the masculine distribution—on upper lip, front and under surface of chin, over spines of scapulae and deltoid regions, outer surface of upper arms, forearms, lower abdomen (where the pubic hair extended up as far as the umbilicus), buttocks, thighs, and legs. The abdomen was protuberant and lax, and the skin showed recent and old lineae. The left prepatellar bursa was acutely inflamed and was distended by thin sanious pus.

The superficial fascia of the scalp contained an excessive accumulation of fat. The calvarium was appreciably softened, the diploe appearing to be very vascular. The cerebrospinal fluid was clear and not under increased pressure. The dura mater was unduly adherent to the vault of the skull and was separated from the inner table with difficulty; it was not adherent to the pia-arachnoid. The vessels of the dura mater and those of the surface of the brain were deeply congested, but showed no other changes. There was slight thickening of arteries of Circle of Willis. The sinuses of the dura mater were normal. The brain weighed 1,155 grm. and appeared normal on section; the convolutions were not flattened.

The pineal gland (weight 0.11 gm.) was normal.

The pituitary gland was enlarged, in particular the right lateral portion; so that the infundibulum, which was thickened, was attached to the gland at a point nearer to the left than to the right border. Section showed that this enlargement was due to the presence of a soft, pale yellow, oval tumour which was situated chiefly in the right half of the anterior lobe (Plate 8, Fig. 4). The tumour measured 0.6 by 0.5 cm. There were slight adhesions between the portion of dura mater which forms the floor of the pituitary fossa and the anterior lobe in the immediate neighbourhood of the tumour. The dimensions of the pituitary gland were as follows: greatest transverse diameter, 1.6 cm., the infundibulum being 0.6 cm. from the left border; greatest antero-posterior diameter, 1.1 cm.; greatest vertical diameter, 0.8 cm. The organ weighed 0.9 gm. The pituitary fossa appeared normal, and the clinoid processes were unaltered. The optic chiasma and optic nerves appeared normal, as were also the cavernous sinuses. The sphenoidal air sinuses were healthy.

The thyroid gland was slightly enlarged (weight 60 gm.). The lateral lobes were nodular, and on section showed an increase of colloid substance, but no other important change.

The parathyroid glands appeared normal.

The larynx showed a moderate degree of acute oedema and congestion. The trachea and bronchi were congested, the latter containing muco-pus. There was a total empyema of the right pleural cavity, with complete collapse of all three lobes of the lung. The base of the left lung was partially collapsed, the remainder of the organ being deeply congested and oedematous. No pneumonic consolidation was present in either lung.

The thymus gland was represented by a small mass of fibro-fatty tissue in front of the upper part of the pericardium.

The pericardium was healthy but contained an excess of free fluid. All chambers of the heart were dilated, especially those on the right side. The heart muscle was somewhat soft and flabby, and showed fatty infiltration in the region of the apex of the right ventricle. No myocardial scars were seen. The left ventricle was moderately hypertrophied. The valves of the heart were healthy. The coronary arteries were distinctly thickened, remaining patent when cut transversely; there were no thrombotic occlusions. The aorta showed fatty streaking of the intima immediately above the aortic valve. The heart weighed 370 gm.

The mammary glands presented a condition of marked atrophy, the parenchyma being practically wholly replaced by fat.

The subcutaneous fat of the anterior abdominal wall was three to four inches in thickness. The peritoneum was healthy, no adhesions or free fluid being present. The fat depots of the peritoneum, e.g. the great omentum, mesentery and perirenal fatty tissues were markedly overloaded with fat.

The stomach was deeply congested and mild catarrh was present. The small and large bowels were healthy. The appendix was congenitally absent, being represented by a fibrous nodule in the medial caecal wall at the termination of the anterior longitudinal muscular band.

The liver was enlarged and showed venous congestion of the 'nutmeg' type. It weighed 2,300 gm.

The gall-bladder showed early cholesterosis.

The pancreas was infiltrated by fat but otherwise was apparently healthy.

The spleen was slightly enlarged and deeply congested and weighed 160 gm. The Malpighian bodies were not unduly conspicuous.

The suprarenal glands were enlarged, in particular the right, which showed extensive haemorrhage into the medulla and cortex. Extravasation of the blood had also taken place into the periadrenal fatty tissue. A small haemorrhage in the left suprarenal gland was confined to the medulla. The dimensions of the suprarenal glands were as follows: right, greatest length, 6.8 cm.; greatest breadth, 3.8 cm.; greatest thickness, 1.6 cm.; weight 21.2 grm. Left, greatest length, 5.9 cm.; greatest breadth, 3.6 cm.; greatest thickness, 1.5 cm.; weight, 14.3 grm.

The kidneys were deeply congested, but showed no other important changes, except slight thickening of the main vessels. The right kidney weighed 140 grm., the left 150 grm. The renal pelves, ureters, and bladder were healthy.

The ovaries were normal.

The uterus was healthy. The external os was transverse in outline and slightly patulous. The lateral walls of the vagina near the vault contained several clusters of minute cysts.

A slight degree of generalized arterial sclerosis was present.

*Microscopic examination.* 1. *Pituitary.* Basophil adenoma of the anterior lobe. The cells of the tumour were arranged in groups, many around thin-walled blood-vessels and blood-spaces. Several large blood-sinuses were present (Plate 8, Fig. 5), in size much larger than those of the normal anterior lobe. Supporting intercellular connective tissue and stroma were scanty and in most places non-existent. Very slight degenerative changes were present in the centre of the tumour. A very thinned out layer of anterior lobe substance covered the outer surface of the tumour and was compressed so as to appear laminated. At certain areas at the periphery of the adenoma there were elongated strands of fibrous tissue as if an attempt had been made at encapsulation but without success. On the whole the line of demarcation between the adenoma and the substance of the anterior lobe, as shown by specific granule stains, was very clear. The cells of the tumour were of irregular shape, but in many groups it was impossible to make out the line of demarcation between individual cells. Most of the nuclei (Plate 8, Fig. 6) stained very deeply, but others, especially in certain areas, were vacuolated or ring-like with a central pale area. The nuclei varied greatly in size and shape, most being irregular or angulated. Multinucleated cells were fairly common. Mitoses were scanty. The pars intermedia and pars posterior were normal.

2. *Thyroid.* Vesicles dilated—a few cystic. No epithelial hyperplasia. Excess of colloid. Changes were those of early colloid goitre.

3. *Parathyroid.* Amorphous deposits of calcium. Practically no evidence of reactive change around the deposits. Histology otherwise normal.

4. *Thymus.* Completely replaced by fibro-fatty tissue. No Hassal's corpuscles seen.

5. *Pineal.* Normal histology.

6. *Suprarenals.* Deeply congested. Hyperplasia of cortex, with, on right side, haemorrhage. Greater part of medulla of right suprarenal replaced by haemorrhage of very recent origin. Haemorrhage also in medulla of left suprarenal but not extensive.

7. *Ovary.* Interstitial cells inconspicuous. Occasional small deposits of calcium immediately beneath the tunica albuginea. Arterial sclerosis.

8. *Pancreas.* Lipomatosis, with slight interstitial pancreatitis. No important change in parenchyma or islet tissue. Arterial sclerosis.

9. *Kidney.* Chronic venous congestion. Arterial sclerosis and arteriolar

sclerosis. Degeneration of many glomeruli. The lumens of several collecting tubules contained amorphous deposit of calcium.

10. *Spleen.* Marked venous congestion of comparatively recent origin. Hyalinization of central arteries of Malpighian bodies.

*Splenic artery.* Marked arterial sclerosis with fibrosis and extensive calcareous deposits in thickened media. Fibrous thickening of adventitia. No appreciable thickening of intima, but in parts, reduplication of internal elastic lamina.

11. *Liver.* Well-marked chronic venous congestion. Fatty infiltration. Arterial sclerosis of branches of hepatic artery. Marked leucocytic infiltration of many of the portal spaces.

#### *Comments.*

The presence of the basophil adenoma was diagnosed on the clinical appearances. We are aware, of course, that in the past such symptoms and signs as our patient showed, have been ascribed to adrenal tumours, and that it was thought impossible that such a small tumour as a basophil adenoma could produce such striking changes. But the size of an adenoma of an endocrine gland is no index of its activity in producing hormones.

Further, it has long been known that a pituitary tumour could produce changes in the other glands of the endocrine series, especially in the adrenals and the thyroid. Experimentally it has been shown by Collip (3), (4), that there are both thyrotropic and adrenotropic fractions in extracts of the anterior pituitary lobe.

The only adenomatous structure found in our case was in the pituitary, and we believe that the adrenal and thyroid changes were secondary.

Our findings would give support to the view that a basophil adenoma of the pituitary body gives rise to a condition that can be recognized clinically.

We wish to thank Professor Shennan for help in the pathological work.

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2. Cushing, H., *Bull. Johns Hopkins Hosp.*, Balt., 1932, l. 137.
3. Collip, J. B., *Lancet*, Lond., 1933, i. 1208.
4. Collip, J. B., *Ibid.*, 1933, ii. 347.

#### DESCRIPTION OF PLATE

PLATE 8, FIG. 1. Photograph before onset of disease.

FIG. 2. Photograph to show adiposity and general appearance and the abdominal striae.

FIG. 3. Photograph to show peculiar condition of the lower legs.

FIG. 4. Antero-posterior section of the pituitary gland showing the adenoma in the centre of the anterior lobe. (Eosin-methylene  $\times 9$ .)

FIG. 5. Section of the adenoma showing its structure and the large blood spaces, (Iron haematoxylin aniline blue fuchsin  $\times 180$ .)

FIG. 6. Section showing granularity of the cytoplasm of the cells and the varied character of their nuclei. (Iron haematoxylin aniline blue fuchsin  $\times 700$ .)



FIG. 1



FIG. 2



FIG. 3



FIG. 4

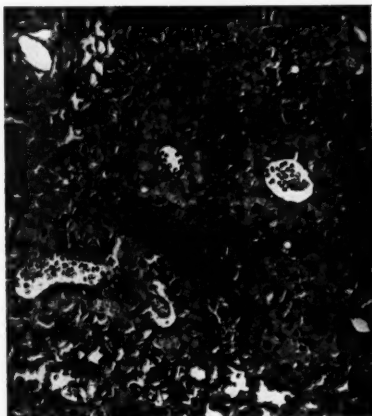


FIG. 5

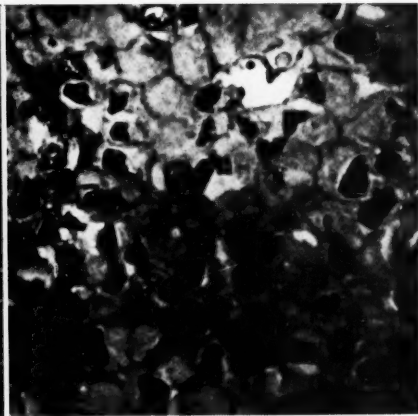
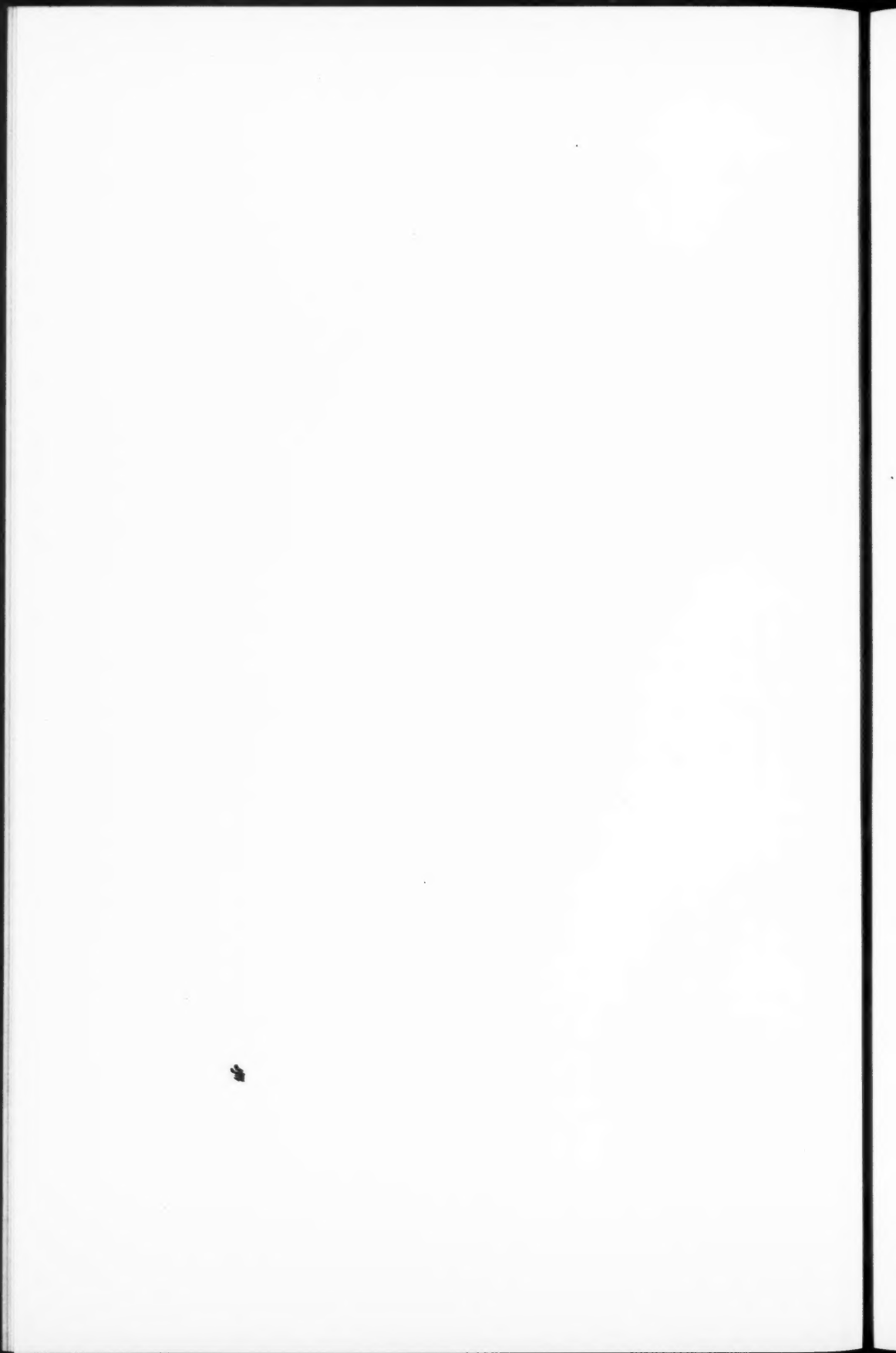


FIG. 6



## BLOOD-UREA CLEARANCE BEFORE AND AFTER GIVING UREA <sup>1</sup>

By FRANK SCOTT FOWWEATHER

(From the Dept. of Pathology and Bacteriology, University of Leeds)

Of the many attempts to express renal function in mathematical terms, the conception of 'blood-urea clearance' introduced by van Slyke and his co-workers (8, 4, 9, 5, 10) appears to be the most promising, and has attracted considerable attention. The van Slyke formulae have the advantage of greater simplicity compared with such formulae as that of Ambard and Weill (1), yet avoid the great practical limitations imposed on the use of the so-called 'urea concentration factor', i. e., the ratio between the concentration of the urea of the urine and that of the blood, introduced by Gréhant (3).

The blood-urea clearance is defined by van Slyke and his co-workers as the volume of blood cleared of urea per minute by the kidneys, or in other words, the volume of blood whose urea content is represented by the urea excreted per minute in the urine.

It has been shown that when the urine volume is fairly large, the urea excretion per minute equals the urea contained in a constant volume of blood, which in a normal adult is about 75 c.c. When the urine volume falls below a certain limit, called the 'augmentation limit' (about 2 c.c. per minute in adults), the urea-excretion rate also falls, and on the average, in proportion to the square root of the volume of urine per minute. Thus, above the augmentation limit, urea excretion proceeds at maximum speed, and the output per minute represents the urea content of a maximum blood volume. This blood volume, called the 'maximum blood-urea clearance ( $C_m$ )' is obtained from the following formula :

$$C_m = \frac{UV}{B}$$

where  $U$  = urea content of urine

$B$  = urea content of blood

$V$  = number of c.c. of urine excreted per minute.

Since, below the augmentation limit the volume of blood whose urea content is represented in one minute's excretion is not a constant, but varies in proportion to the square root of the urine volume, useful data with respect to urea excretion can only be obtained if observations are

<sup>1</sup> Received August 25, 1933.

made with a standard, constant urine-volume output, or if the urea excretion that would accompany such a standard volume output can be calculated from data obtained with any other observed volume output below the augmentation limit. The latter is the only practicable procedure, and, adopting a standard urine volume of 1 c.c. per minute, and making use of the square root rule above-mentioned, it can be shown that, with any observed volume per minute  $V$ , the volume of blood whose urea content is represented by the urea excretion occurring when the urine output is this standard quantity (called the 'standard blood-urea clearance,  $C_s$ ') is given by the formula:

$$C_s = \frac{U}{B} \sqrt{V}.*$$

The data, therefore, that are required for the calculation of blood-urea clearance are the concentrations of urea in blood and urine, and the volume of urine excreted in a measured time. If this volume exceeds 2 c.c. per minute, the maximum clearance is calculated, and if the volume is less than 2 c.c. per minute the standard clearance is calculated. The results obtained from the above formulae are given in c.c. For clinical work it is, however, much more convenient to have the results expressed as a percentage of average normal function. Möller, McIntosh, and van Slyke give line charts from which maximum and standard clearances can be read off directly, either in c.c. or percentage of average normal function, from observed values of  $U$  and  $V$ . It should be added that for children, or others whose

size differs considerably from that of average adults, a correction is introduced by multiplying the observed  $V$  by the factor  $\frac{1.73}{\text{square metres surface area}}$  (see McIntosh, Möller, and van Slyke).

In this country the most widely used single test for the examination of renal function is the urea concentration test of MacLean and de Wesselow (7). Möller, McIntosh, and van Slyke (8) say of this test that 'in the study of nephritic patients, however, the method invites error by neglect of the blood urea'. I (2) had already made a similar criticism, and for some years it has been the practice here to combine blood-urea determinations with the urea concentration test in the manner which has previously been described (2); yet even with such a combination, difficulties in interpretation of results frequently arise, especially when the urine volumes differ greatly from the average, and the van Slyke formulae, since they take account mathematically of the urine volumes, are sure to receive sympathetic consideration as they promise an avoidance of these difficulties.

Some years ago I carried out an investigation in which the blood urea of

\* For the full development of these formulae, as well as for a more detailed treatment of the subject, the original papers should be consulted, or the account given by Peters and van Slyke in *Quantitative Clinical Chemistry*, i. 'Interpretations', 345 (Bailliere, Tindall and Cox).

a number of patients was determined before, and at one, and two hours after giving 15 grm. of urea, as well as making the usual determinations of the urea-concentration test. The investigation did not give results of any real value and was laid aside. Following the appearance of the work dealing with blood-urea clearance, however, it was realized that the data obtained in this investigation could be used for calculating the blood-urea clearance according to the van Slyke formulae.

The values for blood-urea clearance for the first hour-period after giving urea will not be considered, since the blood-urea concentration during this period was not constant. With regard to the second hour-period, however, the figures for blood urea at the beginning and end were approximately equal, so that it appears that, following a rise during the first hour after giving 15 grm. of urea, the blood-urea concentration remains at an approximately constant level for the next hour. This result makes the second hour-period a particularly useful one for studying urea excretion when the blood urea is at a distinctly higher level than when no urea is given. As this approximate constancy of the blood-urea concentration during the second hour-period is the basis of subsequent work, it will be referred to again later.

The results obtained for blood-urea clearance before urea, and during the second hour after, as calculated from the data just mentioned, showed one outstanding feature, namely that, in the case of patients showing no evidence of renal disease, the clearance values during the second hour after urea were concentrated within a decidedly narrower range than the values obtained before urea.

The utility of any method of investigating possible departures from the normal, depends on the narrowness of the limits within which the normal values lie, and any conditions which appear to increase this narrowness are worthy of investigation. The above results do no more than suggest that, under the conditions obtaining during the second hour after urea, the blood-urea clearance values of normal individuals fall within narrower limits than when no urea is given; they cannot be taken as proving this point, for the work described was not originally undertaken for the purpose of calculating blood-urea clearance values. Instructions had been given that urine was to be collected hourly, following the giving of urea, but it was not specially insisted on that the period should be in all cases exactly sixty minutes, or alternatively that the actual time (to the nearest minute) at which each specimen of urine was taken should be stated. Hence it has been assumed that each specimen of urine represented a sixty-minutes' output, though this may not have been exactly true in all cases. Further, the necessity of instructing the patient to empty the bladder completely on each occasion when urine was taken was not specially insisted on, so that incompleteness of emptying the bladder may have occurred. It was therefore decided to repeat the investigation under more carefully controlled conditions. To reduce the number of blood specimens to be taken, advantage was taken of

the fact previously referred to, that the blood urea is at an approximately constant level during the second hour following the ingestion of 15 gm. of urea. As this point is an important one, the actual results relating to it will be given.

In 33 cases the average increase in the blood-urea nitrogen at the end of the second hour, over the value obtained before urea was given was 16.7 mg. per 100 c.c.

Of these 33 cases the number showing differences between the values at the beginning and end of the second hour of less than 5 mg. was 26, or 79 per cent.

The number showing differences of 5 to 10 mg. was 4 or 12 per cent., and 3, or 9 per cent. showed differences slightly over 10 mg.

Thus, if the mean between the beginning and end figures is taken as the average over the period, then the beginning or end figures differ from the average by slightly over 5 mg. in 9 per cent. of cases, by 2.5 to 5 mg. in 12 per cent., and by less than 2.5 mg. in the remaining 79 per cent. It is highly probable, therefore, that a value for blood urea obtained from blood taken at any time during this second hour-period does not, in the great majority of cases differ very appreciably from the average value over the period, and may be used in calculations to represent that average without serious interference with the value of the results obtained.

### *Experimental*

The subjects selected for the second investigation were healthy male medical students, and the tests were carried out in the period between breakfast and lunch, as this is the period recommended by Möller, McIntosh, and van Slyke. The procedure adopted was as follows:

The subject took his ordinary breakfast, usually about 8 a.m. Coffee was forbidden and some other beverage substituted for it. About 9 a.m. he emptied his bladder, noting the time to the nearest minute, and the urine so obtained was rejected. Shortly before 10 a.m. a specimen of blood was taken, and immediately afterwards (the exact time being again noted) the bladder was again emptied. The volume and urea content of this specimen were determined and the values so obtained, with the blood-urea content, were used in the calculation of the blood-urea clearance, 'before urea'. Immediately after the urine had been obtained as above, the subject drank a solution of 15 gm. of urea in about 200 c.c. of water. The bladder was emptied about one hour following the taking of the urea and again about two hours after, the exact time of course being noted in each case, and shortly before the last specimen of urine was obtained blood was again withdrawn. The results of analysis of the last specimen of urine and of blood served for the calculation of the blood-urea clearance during the second hour after the urea was given. It will be referred to as the result 'after urea'.

During the test the subject was allowed to carry out his ordinary student activities in the hospital, interrupting these only to visit the laboratory when specimens of blood and urine were required. There was thus no attempt made to keep him entirely at rest, but his activities were, from the physical standpoint, quite mild.

Fifty subjects were dealt with in this way, and the results are as follows:

The average increase of blood-urea nitrogen during the second hour was 12.8 mg. per 100 c.c., the extreme values being 8.0 and 16.8 mg. In a general way the increase varies inversely with the weight of the subject. The results before urea, calculated as percentages of the average normal of Möller, McIntosh, and van Slyke, cover the range 29 to 107, while those after urea lie between 73 and 120. The distribution of the results is shown in Table I; Figs. 1 and 2 illustrate this distribution diagrammatically. The

TABLE I.

Clearance values. (Per cent. of van Slyke's average normal.)	Before urea. (Cases.)	After urea. (Cases.)
25-30	1	—
30-35	2	—
35-40	—	—
40-45	1	—
45-50	—	—
50-55	—	—
55-60	1	—
60-65	6	—
65-70	3	—
70-75	5	2
75-80	11	11
80-85	8	11
85-90	—	11
90-95	4	4
95-100	3	4
100-105	3	3
105-110	2	3
110-115	—	—
115-120	—	1

results are not corrected for body-weight. In the table no distinction is made between standard and maximum clearances. Actually there were very few of the latter, viz. two cases before urea and three after urea.

#### *Discussion of Results*

The results in Table I amply bear out the suggestion given by the previous series, and conclusively show that the figures obtained for blood-urea clearance in normal individuals after urea occupy a much narrower range than before urea. Further, in addition to the wide range covered by the figures before urea, many of them, viz. 22 out of the 50 results obtained fall below the values (76-120) given by Möller, McIntosh, and van Slyke for healthy persons. On the other hand, the results after urea all fall within

the range 73-120, which is almost identical with the normal range determined by Möller, McIntosh, and van Slyke on a much smaller number of cases. It would appear, therefore, that the urea clearance after urea is a much truer indication of the state of renal function than the value obtained before urea.

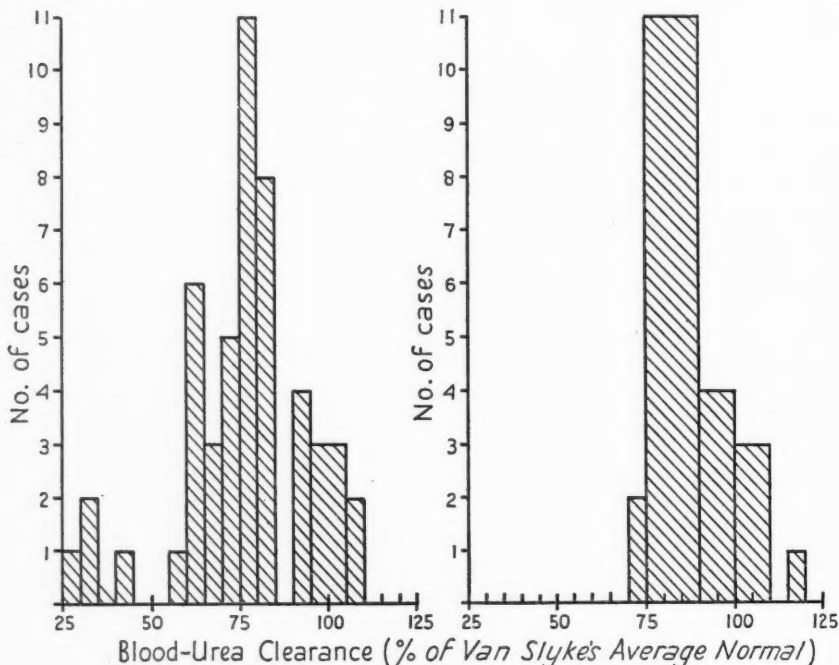


FIG. 1.—Before urea.

FIG. 2.—After urea.

Some other features of the results are of interest. The average value before urea is 75.9; after urea it is 86.8. This is reflected in a comparison of results in individual cases. Thus in 35 cases, the value after urea is greater than before it, while in only 10 is the reverse the case; 5 cases give identical results for both periods. Moreover the difference in the cases giving higher results after urea is sometimes very large—over 60 in 1 case, and between 20 and 60 in 9 others, whereas in the cases giving higher results before urea, the greatest difference is 17, and in 7 of the 10 cases the difference is less than 10.

Yet in spite of the great differences that occur in certain cases, good agreement (differences of less than 10) is seen in 22 of the cases, and fair agreement (differences of 10 to 15) in 9 others. There is thus a suggestion of an essential constancy, upset in a certain proportion of cases by interfering factors.

It is not claimed that the method adopted here for the determination of the blood-urea clearance before urea is precisely the method adopted by

Möller, McIntosh, and van Slyke. The method recommended by these authors, though it does not involve the giving of urea, involves the collection of urine during two successive periods of one hour each, and the patient is kept quiet during the test. It is recommended that the clearance be calculated for both periods, and presumably the average of the two results is taken. The only difference between this method and the one used in the present work, apart from urine collection over two successive hours instead of over one hour, is that in the former the patient is kept quiet during the test, while in the present work he has been allowed to indulge in moderate activity. This activity of the subject in the present work cannot be responsible to any great extent for the large number of low results obtained before urea, for, as will be shown later, similar results have been obtained in patients who have been kept in bed throughout the test.

The reason given for the recommendation that urine should be collected over two successive hours, instead of one, is that the chief source of error is probably the possibility of incomplete emptying of the bladder, either at the beginning or end of a period, and the collection of two urine specimens is considered to afford a check on this factor. No doubt this factor is responsible, to some extent, for error in the present results after only one collection, but examination of the results offers no very strong evidence on this point. It is true that the average volume of urine passed before urea is less than after urea, but examination of individual figures shows no obvious connexion between low urine volumes and low results for blood-urea clearance. Thus of 18 cases which give results before urea below 73, only 5 have volumes of urine less than 0.5 c.c. per minute, 6 have volumes between 0.5 and 1.0 c.c. per minute, and 7 have volumes exceeding 1.0 c.c. per minute. On the other hand, after urea 8 cases with volumes of urine of less than 0.5 c.c. per minute give results between 76 and 107, and 7 with volumes between 0.5 and 0.65 c.c. per minute give results between 80 and 107.

Complete emptying of the bladder at the beginning and end of the period under examination is, of course, essential, if reliable results for blood-urea clearance are to be obtained, and the giving of urea has probably an important influence on this point. The volumes of urine in the 50 cases before urea average 0.78 c.c. per minute, while in the second hour after urea the average is 1.22 c.c. In 43 of the 50 cases, the volume after urea exceeds the volume obtained before urea. The volume of urine passed during the first hour after urea was not measured in the earlier cases, but in the last 28 cases it was found to give an average of 1.69 c.c. per minute, and in every case in which it was measured it exceeded the volume obtained before urea. These facts probably account, to some extent, for the more uniform results after urea than before. For since there is, in general, a greater volume of urine secreted during each of the periods following the urea than before it is given, there will be a more satisfactory stimulus to the bladder to empty itself at the beginning and end of the second hour, and emptying is likely to be more complete at these times; and even where emptying is not complete,

the relative error due to this cause will be less when big volumes are secreted than when the volumes to be dealt with are small.

But the fact that, without urea, small volumes of urine may be obtained, is not the cause of abnormally low clearance values in all cases; this is shown by the lack of correspondence between low urine volumes and low clearance values. There must be some other factor involved in the giving of urea that exerts an important influence towards the production of uniform results. This factor is probably the raising of the blood-urea concentration. It is known that the blood-urea concentration is one of the principal factors governing urea excretion. There are, however, many other factors, not all of them clearly understood, yet capable, no doubt, of causing considerable variation in the value for blood-urea clearance. Increasing the blood-urea concentration therefore increases the magnitude of this factor and its influence on urea excretion relative to the other possibly interfering factors, and it is probably in this way that greater uniformity in results is obtained by calculating blood-urea clearance after giving urea in the way I have described.

If, then, the giving of urea exerts its effect in the way just mentioned, in addition to causing the production of larger volumes of urine, and therefore more satisfactory emptying of the bladder at the beginning and end of the period under observation, or minimizing errors due to complete emptying, the results obtained after urea will be more satisfactory than when obtained without urea, even though certain errors may be avoided by carrying the collection over two successive hours. There is no doubt of the advantage of the calculation of blood-urea clearance after urea over that before urea, in the method of the present work.

The results so far described, then, show that values for blood-urea clearance obtained over one-hour periods without giving urea, give, in an appreciable proportion of presumably healthy persons, results which are decidedly below what are considered to be normal, while after urea not only do the results fall within the normal range, but the average result after urea is higher than the one before it. The question therefore arises as to what is the effect of giving urea for determining the blood-urea clearance of patients whose renal function may be impaired. Is the tendency to give a higher value after urea such as to cause results to be lifted into the normal range, when, in fact, the true value should be below it? Further, there is the question of exercise to be considered. Can the discrepancies between the values before and after urea in normal subjects be due to the fact that moderate exercise during the test has been allowed, though the conditions laid down by those responsible for the introduction of the test specify that the subject should be kept at rest?

To investigate these questions the tests have been carried out on hospital in-patients who are confined to bed. The subjects include patients in whom there is no evidence of renal disease, and patients in whom some form of renal disease is believed to be present. It has been my object in making

these tests not only to compare blood-urea clearance before and after urea, but also to compare these results with those given by the renal function test previously in routine use. This comprises the determination of the resting blood urea, followed immediately by a urea-concentration test, and the conditions used in this test have been maintained throughout the present investigation. Thus the patient takes no food from the evening of the day preceding the test, and very little fluid. This restriction of fluid was introduced to limit the tendency to give large volumes of urine during the urea-

TABLE II

Patient.	Age.	Blood-urea clearance.		Diagnosis.
		Before urea.	After urea.	
1 Alice C.	32	39	82	Osteitis fibrosa.
2 Emily J.	47	54	82	Hyperthyroidism.
3 Charles E.	32	74	83	Nervous vomiting.
4 Stanley C.	45	82	73	Vitreous haemorrhage.
5 Kathleen B.	24	71	95	Cerebral tumour. (Death 16 days later. At autopsy small glioma of sup. corp. quadrigemina found.)
6 Doris M.	38	55	78	Dyspepsia.
7 Benjamin R.	62	90	85	Diabetes.
8 Alice T.	54	76	76	Hyperchlorhydria.
9 Charles T.	35	66	74	Dyspepsia.
10 Joseph L.	47	61	86	Polyarthritis.
11 Florence S.	—	86	120	Morning vomiting with pregnancy; subsequently cleared up.
12 Edith S.	—	49	81	Morning vomiting with pregnancy; subsequently cleared up.
13 Bernard C.	63	65	69	Nervous dyspepsia.
14 Elizabeth R.	28	65	96	Retinitis proliferans.
15 Kathleen H.	12	76	76	Delinquency and backwardness; no unhealthy signs apparent.
16 Elsie R.	19	82	85	Fibrositis.
17 Sarah R.	59	28	65	Otosclerosis.
18 Ethel B.	46	48	70	Atrophic gastritis.
19 Elizabeth O.	50	66	72	Vertigo—(considerable improvement in a few days and patient discharged apparently well).
20 William H.	26	87	88	Functional albuminuria.

concentration test, as it is found that where large volumes of urine are obtained the difficulties in interpreting the results are much increased. On the morning of the test the bladder is emptied about 8.30 a.m. About 9.30 a.m. blood is taken, following which the bladder is again emptied. Fifteen grams of urea in about 200 c.c. of water are then given, and the bladder is emptied at one hour, and again at two hours after taking the urea. The only addition to this routine procedure which is required to obtain blood-urea clearances before and after urea, is that blood is again taken towards the end of the second hour, usually about 11.15 a.m. The

time, to the nearest minute, at which each event occurs is noted. The patient is specially instructed to empty the bladder as completely as possible on each occasion on which urine is passed, and the total volume of each specimen is carefully preserved for measurement. The procedure during the actual test is therefore the same as that adopted in the investigation of students, but unlike the latter case is preceded by abstention from food and limitation of fluid intake from the previous evening.

TABLE III.

Patient.	Age.	Blood-urea clearance.		Diagnosis.
		Before urea.	After urea.	
1 John R.	31	42	52	Chronic bone tuberculosis; parenchymatous nephritis. (Subsequently died; at autopsy subacute nephritis; sinus from tuberculous disease of 5th lumbar vertebra and sacro-iliac region.)
2 Florence H.	23	46	57	Acute nephritis.
3 John P.	36	60 36	48 (20.2.33) 50 (16.3.33)	Albuminuria; oedema— ? subacute nephritis.
4 Dorothy E.	17	5.4	6.5	Renal rickets.
5 Roy C.	17	39	12	Renal rickets.
6 Mary W.	58	8.7	9.5	Polycystic disease of kidneys.
7 Jack T.	29	8.4	11.5	Chronic nephritis. (Subsequently died; no autopsy.)
8 Mrs. W.	—	22	42	Pregnancy; persistent albuminuria; pyelitis.
9 Eliza A.	47	36	45	? Polycystic disease of kidneys.
10 John H.	34	21	14.2	Chronic interstitial nephritis.
11 Ivy H.	20	35 31	49 (2.1.33) 45 (25.7.33)	Acute nephritis becoming chronic.
12 Ernest G.	25	33	37	Acute exacerbation of chronic nephritis.
13 George P.	35	50	52	Acute nephritis, becoming chronic.
14 Charles W.	37	41	47	Interstitial nephritis.
15 Christine M.	29	34	42.5	Pyelitis.
16 Rose W.	58	58	56	Chronic nephritis.
17 Emma K.	62	30	9.5	Hypertension; epistaxis. ? chronic nephritis.
18 Joe S.	22	58	57	Chronic nephritis.
19 Ada G.	60	48	52	Granular kidneys; chronic uraemia.
20 Mary K.	23	31	33	Acute nephritis.

The results on patients in whom renal disease is believed to be absent are shown in Table II, and those on patients believed to be the subject of renal disease are in Table III.

The results in Table II are very similar to those given by healthy students. In 15 out of the 20 cases the result after urea is greater than before; in 3 the 2 results are practically identical, and in only 2 is the result after urea

lower than before. Moreover the result before urea in 7 of the cases is 55 or less, i.e. is very definitely below the normal range, while in each of these cases the result after urea appears to be indicative of normal renal function.

The results after urea fall within the range 65 to 120, and 17 of the cases give results between 73 and 120, which are the limits of the results after urea found in the students. Of the remaining 3, 2, giving values of 69 and 65, were elderly patients (63 and 59 years respectively), and the third, a patient of 47, gave a value of 70.

The great similarity of these results to those obtained on healthy students rules out the possibility that the mild exercise permitted to the students during the test is the cause of the frequent, and sometimes very considerable difference between the results obtained before and after urea. The results also indicate that abstention from food and limitation of fluid intake from the evening before the test have little or no influence on the type of result obtained.

In Table III there is again a preponderance of cases in which the result after urea is greater than before, though not quite so marked as in Table II. Out of the 22 results shown this occurs in 12, while in 6 the 2 results are practically identical (differences of not more than 2), and in 4 the value obtained after urea is less than before. But in none of these cases does either figure reach a value which might be considered normal.

There is, then, with nephritic patients, as well as with other patients and healthy students, still a tendency to obtain higher results after urea than before, but in no case of renal disease so far dealt with (including, besides the cases in Table III, a number of others tested after the table was compiled) does the figure after urea reach what must be considered a normal value.

The results on normal students and on patients without any recognizable renal disease have already shown that the urea clearance obtained after urea is a better indication of the state of renal function than the clearance obtained before urea, and the results on patients with renal disease offer no evidence to the contrary.

It is clear, then, that where the value obtained after urea falls within the normal range, the value before urea can be disregarded. But what of cases in which the value after urea is low, but that before urea is within the normal range? Three such cases, not included in Table II or Table III have occurred. The results are shown in Table IV.

TABLE IV

Patient.	Age.	Blood-urea clearance.		Diagnosis.
		Before urea.	After urea.	
1 Joseph D.	47	79	62	Optic neuritis.
2 Eliza P.	64	104	59	Diabetes.
3 Joseph O'D.	62	71	37.5	Malignant disease of right kidney.

Some further details regarding these cases are of considerable interest :

No. 1. This patient attended the eye department and was found to be suffering from optic neuritis. It was also discovered that his blood gave a positive Wassermann reaction, and he was transferred to the venereal diseases department.

His blood-urea nitrogen, before giving urea, was 29.1 mg., i.e. was definitely raised.

No. 2. This patient, in addition to evidence of diabetes mellitus, also showed slight albuminuria, some enlargement of the heart with accentuation of the aortic second sound, and a definitely raised blood-pressure (220/110).

No. 3. The clearance test on this patient was performed on April 5. On May 1 the right kidney was removed. The upper half was found to consist of a tumour which proved to be an adeno-carcinoma. Death occurred on May 9, and at autopsy it was found that the left kidney was very pale, showing marked increase of pelvic fat and some diminution of cortex; it weighed only three ounces.

In all three cases, therefore, there is evidence against the assumption that the kidneys are normal, and it would seem at least as reasonable to accept the clearance values obtained after urea as a true indication of the state of renal function, as to assume, from the clearance values, before urea, that in each case renal function is unimpaired. These cases, therefore, cannot be considered as offering any real evidence against the conclusion already supported overwhelmingly by the results on healthy students and on patients without renal disease, that the clearance values after urea are a truer indication of the state of renal function than clearance values before urea.

From all the foregoing results there seems to be sufficient justification for dispensing entirely with the calculation of clearance values before urea. This will result in some simplification of the test. I would not suggest that the bladder be emptied only at the beginning and end of the second hour-period after urea. By instituting the hourly emptying of the bladder before the second hour-period arrives, there seems to be more satisfactory emptying at the beginning and end of this period than when no preparation for urine collection before this period is made. The test might therefore be carried out as follows :

At 7 a.m. the patient may be allowed a light breakfast; coffee must be avoided, but tea, if weak and in small quantity, may be permitted. At 9 a.m. the bladder is emptied, and immediately afterwards the urea is given. At 10 a.m. the bladder is again emptied. At about 10.45 a.m. a specimen of blood is taken for urea determination, and at 11 a.m. the bladder is again emptied. Each specimen of urine is to be accompanied by a label on which is entered the time, to the nearest minute, at which each specimen has been passed. The clearance value is, of course, calculated from data obtained from the third urine specimen (exact volume, exact time of secretion, to nearest minute, and urea concentration) and the blood specimen. If desired, the results of a urea-concentration test may also be obtained by

determining the urea in the first and second urine specimens also. It is not necessary to keep the patient in bed during the test.

We must now return to a consideration of what is to be taken as the normal range for blood-urea clearance obtained in this way. The results on healthy students have already been indicated. The twenty cases of Table II are admittedly a small number from which to draw conclusions, but on the whole the results agree very well with those obtained on the students. It would seem, therefore, to be a satisfactory interpretation of the results to regard any value over 70 as normal, except in elderly subjects, for whom a somewhat lower limit must be allowed, say 65, from about the end of the fifth decade.

*Comparison of Results of Urea Clearance Test with Routine Renal Efficiency Test*

The criteria of normal renal function in the routine test dealt with have been regarded as a blood-urea concentration within normal limits, together with a concentration of urea in the urine during the first or second hour following the usual dose of urea, of 2 per cent. or more; or if the blood urea is raised, this should be accompanied by an increase in the urine-urea concentration in approximately the same proportion as the increase in the blood urea.

The normal blood-urea nitrogen, according to MacKay and MacKay (6) includes values up to 23 mg. per 100 c.c. of blood. Eight of the cases in Table IV show blood-urea nitrogen values either below 23 mg. or only slightly above, with urea concentrations in the urine taken during the second hour after giving urea of over 2 per cent. Details of these cases are in the following table (Table V).

In all these cases our routine test, judged by the criteria just mentioned, fails to show any impairment of renal function, yet all give a blood-urea clearance very definitely below the normal range. A consideration of the considered diagnosis given in Table III, together with the additional findings in Table V, leaves no doubt that the blood-urea clearance value is the more correct index of the true state of the kidneys, and one is forced to the conclusion that a negative result to the urea-concentration test, even when considered along with the blood-urea concentration is unreliable as an indication of a satisfactorily functioning renal apparatus, and that it is insufficient to consider blood- and urine-urea concentrations only; the volume of urine secreted over a given period must also be taken into account in a very precise manner, such as is allowed for in the van Slyke formulae.

The determination of the blood-urea clearance after urea seems likely to prove a valuable method for the investigation of renal function, but its true value can, of course, be assessed only from the accumulation of further experience of its use.

TABLE V

No. of case in Table III.	Blood-urea nitrogen (mg. per 100 c.c.).	Urea concentration in 2nd hr. urine (%).	Clearance values.		Other findings.
			Before urea.	After urea.	
2	18.1	2.18	46	57	Albuminuria; granular and cellular casts.
9	23.3	2.03	36	45	Albuminuria; granular casts.
13	21.1	2.35	50	52	Had previously all the signs of acute nephritis; some albuminuric retinitis and slight increase of blood-pressure with some blood in urine remained at time of test.
14	24.3	2.72	41	47	Vomiting; albuminuria and granular casts.
15	17.7	2.92	34	42.5	Pus and blood in urine; marked albuminuria.
16	23.4	4.20	58	56	Albuminuria; raised blood-pressure.
18	22.6	2.04	58	57	Previous history of acute nephritis—5 months in hospital. Now marked albuminuria, granular casts.
19	23.4	3.19	48	52	Previous history of nephritis; now dizziness, headache, vomiting; cardiac hypertrophy, some arteriosclerosis, raised blood-pressure, albuminuria.

### Summary

1. The blood-urea clearance of van Slyke and his collaborators has been calculated for a number of patients from data previously obtained in another investigation. The calculation was applied, not only to a period when no urea was given to the patients, but also to the second hour after administering 15 gm. of urea. The blood-urea clearance of persons without recognizable renal disease appeared to be much more constant after urea than before it.

2. Examination of the data just referred to showed that blood-urea concentration during the second hour, after giving 15 gm. of urea, is approximately constant during this period. This fact facilitates the determination of blood-urea clearance after giving urea.

3. The comparison of blood-urea clearance before and after urea was repeated under more carefully controlled conditions on fifty healthy male students. The results before urea cover a very wide range, and a very large proportion fall below what are considered to be normal values, whereas the results after urea occupy a comparatively narrow range, almost identical with the normal range determined by the authors above mentioned.

4. The reasons for the greater constancy of results following administration of urea are discussed, and it is believed that blood-urea clearance calculated for the second hour after urea is less liable to error than the

clearance calculated over two successive hour-periods without giving urea, as was originally recommended.

5. A similar comparison of blood-urea clearance before and after urea has been made on a number of hospital in-patients, some of whom showed no evidence of renal disease, while others were suffering from renal disease.

6. A study of all the results leads to the conclusion that blood-urea clearance after urea is a more correct indication of the state of renal function than the blood-urea clearance before urea. Consequently, in investigating renal function attention should be paid only to the blood-urea clearance after urea, and a suitable method for its determination is described.

7. The normal range for blood-urea clearance after urea is considered in the light of all the results obtained.

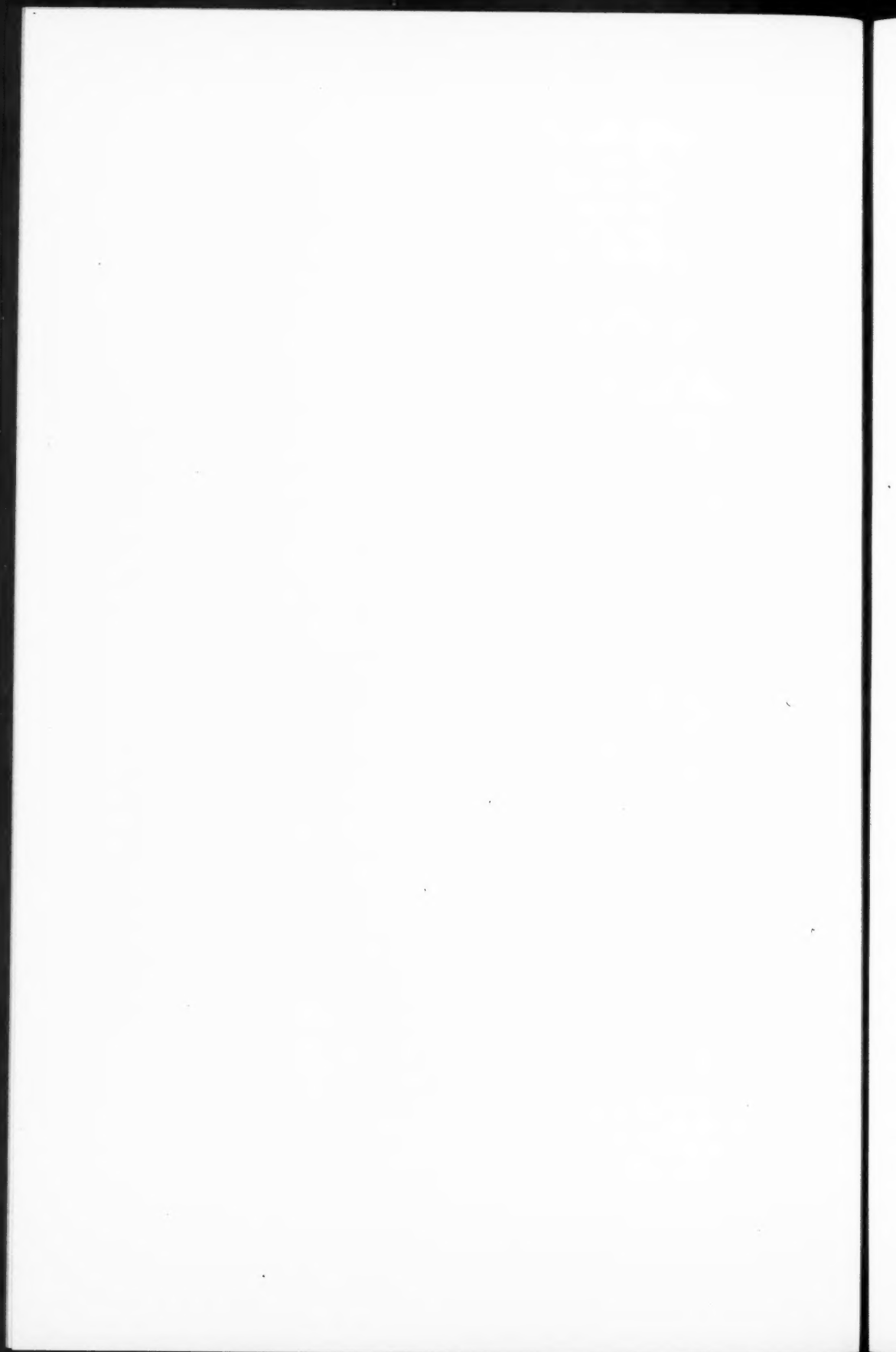
8. The results of the urea-concentration test, considered together with the blood-urea concentration, failed to show any evidence of impaired renal function in a number of cases in which the blood-urea clearance after urea was very definitely below normal. A consideration of all the evidence available supports the view that the blood-urea clearance is the more correct indication of the true state of affairs.

9. It is believed that the determination of blood-urea clearance after urea is a very promising method for the investigation of renal function.

I wish to express my sincere thanks to the honorary staff of the Leeds General Infirmary for permitting me to carry out tests on their patients, and for access to the notes on their cases; to the students who acted as subjects for the investigation, and to the nursing staff for their willing and skilful co-operation.

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## A FURTHER NOTE ON THE PLASMA CHOLESTEROL IN NEPHRITIS <sup>1</sup>

By JAMES MAXWELL

NEARLY six years ago the writer published, in this Journal (1928, xxi, 297), the results of a study of the plasma cholesterol in a series of 181 cases of renal disease of various types. The conclusions which were reached may be summarized as follows:

1. The plasma cholesterol is almost invariably increased when oedema of the renal type is present. The increase may be so slight as only to become apparent when the patient is investigated on several occasions, for the plasma cholesterol is found to fall as the oedema disappears.

2. In acute nephritis with oedema the plasma cholesterol is raised in proportion to the amount of the oedema. During the recovery stage the oedema first clears up, the plasma cholesterol next returns to normal, and lastly, the albumin practically disappears from the urine. In any case of nephritis with oedema the persistence of the plasma cholesterol above the upper normal limit foretells a chronic course of the disease.

3. In acute nephritis without oedema, the plasma cholesterol is always normal, and is, therefore, of no diagnostic or prognostic value.

4. In chronic nephritis with oedema, the plasma cholesterol is often greatly increased, and the amount of cholesterol increase is in no way proportional to the degree of oedema.

5. A persistently raised plasma cholesterol in patients who have been oedema-free for a long period is often associated with the early onset of uraemia. When, however, uraemia develops, the cholesterol figure usually falls to normal.

The purpose of the present paper is to test the suggestion made with reference to the possible prognostic significance of the plasma cholesterol in the oedematous types of nephritis, and with this end in view the cases which were originally investigated six years ago have been followed up. In the original series, forty-two of the cases either were oedematous to a greater or lesser extent at the time of the investigation, or had exhibited renal oedema at some stage of their illness.

*Terminology.* In any discussion upon the subject of kidney disease, the chief difficulty is one of terminology, nor does there appear to be any immediate prospect of a solution of this problem. In the previous paper the use

<sup>1</sup> Received October 13, 1933.

of special terms was avoided as far as possible, and an attempt was made to indicate, by means of tables, the chief clinical feature of each group, also of each individual case. This system has been followed in the present instance, and the cases are arranged in groups, which are comparable with those published previously.

The method used for the cholesterol estimations was the same as that employed in the original investigation, namely, the modification described by McAdam and Shiskin of the Myers and Wardell technique; the normal values are still accepted as being between 0.13 and 0.20 grm. per cent., although even wider limits are accepted as normal by some authorities.

Of the forty-two cases which constituted the groups detailed above, the present state of thirty-five is known; the remaining seven cases have not been traced. A summary of the present condition of these cases compared with that reported in 1928 is given in Table I.

TABLE I

Group.	Cases.	Present state.		Died.	Not traced.
		Clinically well.	Nephritis still active.		
1. <i>Acute nephritis.</i>					
(a) With oedema.	8	6	0	1	1
(b) In which oedema had recently been present.	4	4	0	0	0
(c) 'Healed' nephritis.	4	3	0	0	1
2. <i>Chronic nephritis.</i>					
(a) With oedema when first examined.	14	2	0	10	2
(b) Without oedema when first examined.*	9	0	1	5	3
2a. <i>Uraemia.</i>	3	0	0	3	0

\* In one case, originally included in this group, oedema was never definitely known to have been present, although otherwise the case presented features more suggestive of this type of disease than of any other. As the present paper is concerned entirely with the type of nephritis characterized by renal oedema, this case (No. 98) has been omitted.

A more detailed study of the present condition of these cases is presented in further tables. In order to facilitate comparison with the previous condition, the numbers of the cases in the original series are appended.

*Group 1. Acute nephritis.* (a) Cases in which oedema was present at the time of the first examination (Table II)—eight cases.

The present state of seven out of the eight patients in this sub-group is known. Three have reported for examination, and in each case there is no evidence of present renal disease; in one case a report has been received from the patient's doctor supplying the essential particulars, two other patients have reported that they are in good health, and one patient has not been traced. The investigations in the last case of this group, No. 181, were only recently begun when the former paper was written, otherwise it would not have been included under this heading. The illness began abruptly with

oedema and haematuria, which improved in the first month, although complete recovery did not take place. During this period the plasma cholesterol fell from 0.39 to 0.24 per cent., from which point no further observations were included in the original records. The oedema returned soon afterwards, however, and the plasma cholesterol rose to 0.46 per cent. The patient developed erysipelas three months later and died.

The present position of the cases in this group, therefore, is that out of the seven patients of whom the present state is known six appear to be well; the one patient who has died is now thought to have been incorrectly included in this group, but the chronic state of the disease became apparent from the clinical state rather than from the plasma cholesterol estimations. The study of the plasma cholesterol figures shows that very little information of value has been gained with regard to prognosis. Comparison of the initial plasma cholesterol with the period during which oedema was present indicates that the latter is roughly proportional to the former, yet this may merely be another way of expressing the fact that the rise in the plasma cholesterol is proportional to the degree of oedema in the early stages of the disease, and that the greater the initial degree of oedema, the longer will the patient take to recover. It would appear, therefore, that in acute nephritis with oedema the plasma cholesterol is of less prognostic value than is a careful clinical study of the patient.

(b) Cases in which the oedema had disappeared shortly before the first cholesterol observations were made (Table IIA)—four cases; and cases previously oedematous in which there was no evidence of active nephritis at the time of the first cholesterol estimation (Table IIB)—four cases.

These cases may be considered together, as none exhibited renal oedema while under observation, and the seven patients who have been traced are all apparently well.

In these groups, again, the plasma cholesterol estimation has been of little positive prognostic value, although the fact that the figures are still normal in each case is consistent with the clinical observation that the renal lesion appears to have healed. This point is perhaps of importance for, in some cases of chronic and persistently active nephritis, the plasma cholesterol remains raised in the absence of clinical oedema, although it must be agreed that in every case of this type reported in the following group, there was ample evidence of the activity of the renal lesion on a clinical examination of the patient.

*Group 2. Chronic nephritis. Twenty-three cases.* In all these cases the patients had been oedematous at some stage of their illness, although oedema was not invariably present at the time of the first cholesterol estimation. For purposes of comparison the cases are separated into two sub-groups on the basis of this distinction in Tables III and IIIA.

*Group 2a. Chronic nephritis with uraemia.* Finally there are the three cases in which oedema had previously been present and which were already uraemic at the time of the first investigation. Each of these died before

the publication of the previous report, and they need not be further considered.

Consideration of Table III shows that, with one exception, the plasma cholesterol was considerably raised in each of the cases, nor did it ever become consistently normal when their progress was followed. The figures, however, varied greatly, and it is not possible to correlate the cholesterol findings with the clinical state nor with the subsequent course of the disease. Only two out of the fourteen cases are known to be alive, and in one of these cases (No. 85) the initial plasma cholesterol, 0.44 per cent., was one of the highest figures found. It does not appear, therefore, that the initial figure is of any prognostic value, but unfortunately this case was not systematically followed up.

The mortality in this group has been very heavy, pneumococcal infections accounting for five deaths, and miliary tuberculosis and uraemia for one each; the cause in one other case is not known. The remaining two cases require further comment. In one (No. 101) there was complete clinical recovery, and the patient was apparently in good health until he developed acute lymphatic leukaemia, from which he died. The post-mortem record merely states that the kidneys were 'typical of lymphatic leukaemia', from which it may be inferred that no gross degree of contraction had occurred. Apart from this intercurrent condition, the case might possibly have been included as a complete recovery. The other case (No. 27) was anomalous in that there was albuminuria up to 0.6 per cent., with slight oedema of the legs but without other evidence of heart failure, and it was included as one of chronic renal disease, although the plasma cholesterol result, 0.10 per cent., was quite exceptional. The patient died on the following day, and there was no post-mortem examination, so that the final diagnosis is doubtful and no deductions can be drawn from this case.

The cases in Table IIIA exhibited evidence of chronically active renal disease at the time of the investigation, although oedema was no longer present. In these, therefore, the prognosis was fairly apparent, and only one patient is known to be alive at the present time. In this case (No. 2), although the patient feels well and is at work, there is obvious clinical evidence that the condition is progressing, and although there has been no further oedema the plasma cholesterol is higher than it was five years ago.

In none of the other eight cases was the plasma cholesterol grossly abnormal, but none of the five patients traced has survived. Death resulted from uraemia in four cases, and from 'pneumonia' in one. It may be noted that in three of the uraemic cases the plasma cholesterol was slightly more than 0.20 per cent. at the time of the investigation, whereas of the six cases in which the plasma cholesterol was normal only one is known to have died in uraemia; but these figures are too small to justify any definite conclusion. They do, however, lend some support to the contention put forward originally that a raised plasma cholesterol in the absence of oedema is a serious prognostic sign which indicates the imminence of gross renal failure.

*Summary*

The subsequent progress of the series of cases of nephritis described six years ago has been investigated, and their present state is considered. In the acute cases the plasma cholesterol appears to be roughly proportional to the degree of oedema, but the probable course of the disease can be estimated as well by the clinical progress as by the chemical test.

In the more chronic types of renal disease, the plasma cholesterol varies within very wide limits, and no satisfactory relation can be demonstrated with the clinical course of the disease. Although there has been a heavy mortality in this group, it can now be recognized that the plasma cholesterol observations have proved of little prognostic value. There is slight ground for the suggestion that an increase in the plasma cholesterol, in the absence of oedema, is an indication of the probable early termination of the case in uraemia.

In conclusion, I am indebted to the Physicians to St. Bartholomew's Hospital for permission to reinvestigate the cases which had been under their care, and also to Miss K. Hare, B.Sc., by whom the majority of the recent cholesterol estimations have been made.

TABLE II. *Acute Nephritis with Oedema in 1926-7*

No.	Total duration of oedema.	Initial plasma cholesterol gram. %.	Alterations in plasma cholesterol.	Present state.		Urine.	Plasma cholesterol gram. %.	Remarks.
				Clinically.	B.P.			
5	7 months	0.31	Fell to normal	Well	145/90	Alb. 0	—	Report from doctor.
40	1 month	0.24	" "	"	130/85	" "	0.18	
55	5 weeks	0.27	" "	—	—	—	—	Not traced.
66	2 "	0.24	" "	"	120/80	" "	0.11	
72	2 "	0.22	" "	"	115/80	" "	0.16	
110	4 months	0.36	" "	Reported well	—	—	—	
180	3 weeks	0.26	1 estimation only	" "	—	—	—	Died May 1927.
181	8 months	0.39	Never fell to normal	—	—	—	—	

TABLE II A. *Acute Nephritis First Examined Soon After Disappearance of Oedema*

128	1 week	0.11	Remained normal	Well	110/70	Alb. 0	—	Cholesterol not estimated on account of pregnancy.
138	3 weeks	0.17	" "	"	115/70	" "	0.10	
145	2 "	0.11	" "	"	120/80	" "	0.21	
157	1 week	0.09	" "	"	115/75	" "	0.15	

TABLE II B. *'Healed' Nephritis*

113	4 months	0.14	Remained normal	Well	130/80	Alb. 0	0.18	
130	1 month	0.15	" "	"	120/80	" "	0.15	
135	3 months	0.15	" "	"	110/70	" ft. trace	0.20	
160	2 "	0.15	" "	—	—	—	—	Not traced.

TABLE III. *Chronic Nephritis—Cases Oedematous at Time of First Investigation*

Case No.	Initial plasma cholesterol gm. %.	Maximum plasma cholesterol gm. %.	Minimum plasma cholesterol gm. %.	Progress.	Remarks.
12	0.37	0.37	0.20	Fluctuations of oedema and plasma cholesterol.	Died after 20 months' illness from miliary tuberculosis.
13	0.34	0.40	0.32	Little variation in general condition. Progressive failure of nitrogen excretion.	Died in uraemia after 4½ years' illness.
27	0.10	—	—	Anomalous distribution of oedema almost confined to the legs.	Died from heart failure after 7 months' illness.
37	0.73	0.73	0.32	Persistent oedema, gradual incomplete fall of cholesterol.	Died after 2½ years' illness. No details.
*79	0.33	0.92	0.30	Fluctuations of oedema and nitrogen retention.	Amyloid nephrosis. Died from pneumococcal septicaemia after 9 years' illness.
84	0.48	0.50	0.30	Persistent oedema.	Died from bronchopneumonia after 4 months' illness.
85	0.44	—	—	Apparent recovery.	Now appears well. No albuminuria. B.P. 150/90, blood urea 0.043 gm. %, plasma cholesterol 0.21 gm. %.
86	0.29	—	—	—	No further details.
101	0.27	—	—	Complete recovery after 8 months' oedema.	Died Oct. 1932 of acute lymphatic leukaemia.
107	0.26	—	—	—	No further details.
134	0.24	—	—	Gradual recovery after 3 months' oedema.	Report from doctor: Well—no albuminuria.
165	0.40	0.45	0.36	Remained oedematous for 4 months.	Died from bronchopneumonia.
177	0.48	0.48	0.40	Fluctuating oedema for 5 years.	Died from bronchopneumonia.
179	0.30	0.47	0.30	Fluctuating oedema for 3 months.	Died from bronchopneumonia and empyema.

\* This case has been fully described *Arch. Dis. Child.*, 1927, ii. 220.

Summary: Cases 14. Alive and apparently well, 2. Died, 10. Not traced, 2.

TABLE IIIA. *Cases Which Had Lost Their Oedema Before the First Investigation*

Case No.	Initial plasma cholesterol gm. %.	Maximum plasma cholesterol gm. %.	Minimum plasma cholesterol gm. %.	Progress.	Remarks.
2	0.15	0.19	0.15	Albuminuria persisted.	Feels well but 0.1 % of albumin in urine and a few R. B. cells and granular casts. Blood-pressure 160/100. Blood urea 0.035 gm. %. Plasma cholesterol 0.32.
24	0.17	—	—	—	No further details.
35	0.23	0.23	0.21	Very gradual progress.	Died in uraemia 11 years after onset of disease.
60	0.22	0.22	0.15	Very gradual progress.	Died in uraemia 11 years after onset of disease.
121	0.14	—	—	—	No further details.
140	0.25	0.25	0.18	Becoming uraemic when first investigated.	Died in uraemia 20 years after onset of disease.
149	0.17	—	—	—	No further details.
167	0.07	—	—	—	Died in uraemia 6 years after apparent onset of disease.
172	0.18	—	—	Slight oedema 5 years before first investigation, followed by occasional puffiness. Blood pressure 210/100 but no albuminuria.	Died from 'pneumonia' in October 1932. No further details.

*Summary: Cases 9. Alive but disease still active, 1. Died, 5. Not traced, 3.*

## CLINICAL AND BIOCHEMICAL OBSERVATIONS ON HUNGER OSTEOPATHY, JUVENILE AND LATE RICKETS (OSTEOMALACIA)<sup>1</sup>

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the Royal Infirmary and University of Glasgow)

With Plates 9 to 11

THE purpose of the present communication is to put on record the data derived from a clinical and biochemical investigation of a case of hunger osteopathy, and corresponding observations on cases of juvenile and late rickets (osteomalacia).

In 1849 Trousseau and Lasègue pointed out the essential similarity of rickets and osteomalacia, disorders which, until then, had been regarded as distinct and unrelated clinical entities. Despite this and the work of Pommer (1885), Cohnheim (1889), Schmorl (1909), and Partsch (1919), to the effect that the underlying pathological processes in rickets and osteomalacia are essentially the same, the one occurring in infancy and in adolescence, the other in adult life, the dual conception of Virchow (1853) is still widely accepted. Virchow considers that in rickets what is firm remains firm, nothing essential being absorbed, but that in osteomalacia what is firm becomes soft. Marchand (1908), Kaufmann (1922), and Hess (1928) attempt to reconcile the two opposing views. Hess (1928) believes that the difference in the pathological lesions are of a quantitative rather than a qualitative nature, and suggests that the terms infantile, juvenile, and late rickets be employed according to the age group affected. We have adopted this classification, inserting in parentheses the older name alongside.

Such a view has also the merit of harmonizing the essentially similar metabolic responses in these conditions to the specific therapeutic agent, vitamin D. In this connexion it appears to be justifiable to assume that this similarity of response indicates that the same pathogenic factor is affecting different age groups.

The report by Hunter (1930) that Turnbull has observed, in histological sections of the bones of a case of renal rickets, pathological changes identical with those found in rickets is of great interest, and, if confirmed, would indicate that similar lesions can be produced by apparently different aetiological factors.

<sup>1</sup> Received August 15, 1933.

*Case 1. Hunger osteopathy.* M. F., female, aged 24 years, was admitted to Glasgow Royal Infirmary in June 1932, complaining of pain in the back, shoulders, and knees of eight years' duration.

*Present illness.* About the age of 16 years this girl first began to experience recurrent pains in the knees, hips, shoulders, and back. She was not greatly incapacitated by these pains, and was able to seek employment. From September 1925 till November 1926 she was employed as a gilder in a pottery which was damp and ill-ventilated. Her dietary at this time was insufficient for her needs. She took no breakfast, and she never drank milk, a dislike to it having existed since the age of 6 years. Though inadequate in all respects, what was consumed was relatively well-proportioned, fresh fruit and butter being included. She began to lose weight and strength, and suffered from increasing pain in the lumbo-sacral region and knees. After a respite at the seaside for a few months, she returned to work in the same pottery, and was employed there continuously for another two years; then, as there was little work in the summer months, she only worked six months in each of the next two years. During these last two years she was quite unable to take any exercise apart from her work, and required to rest immediately she returned home in order to be able to travel to her post each day. She had little appetite for food.

*Previous health.* As a baby she was breast-fed for eleven months. In early childhood she had measles, chicken-pox, and mumps, and at 10 years, scarlet fever. She left school at 14 years, apparently healthy, and commenced work immediately in a furrier's establishment.

*Family history.* The patient is one of a family of five children living in somewhat straitened circumstances. The father is a victim of 'rheumatism', but otherwise the family history is negative.

*Condition on admission.* A puny, undersized, though not abnormally proportioned, fair-haired woman of 24 years; 35 kg. in weight, and 120 cm. in height. The mucous membranes were pale, and blood examination showed a mild secondary anaemia. The angles of the mouth were cracked and raw, but the teeth showed no evidence of caries. The gums were spongy and unhealthy. The skull was not large in proportion to the face: the latter was pinched-looking. There was generalized pain over the dorsal and lumbo-sacral areas of the spine, and very marked tenderness along the lower costal margins, which almost touched the iliac crests posteriorly. There was a moderate degree of dorsal kyphosis, and marked lordosis in the lumbo-sacral region. Some limitation in the movement of both shoulders was apparent, and there was creaking in the right. There was no evidence of a rachitic rosary or of a Harrison's groove. Slight creaking could be detected on movement of both knee-joints. The right calf was thinner than the left. Movements of the knee and hip-joints were full. This was in marked contrast to the spine, which was very rigid. The patient walked rigidly and bent forward, and appeared to have difficulty in lifting her feet clear of the ground. She limped with the right leg. There was no apparent abnormality of the thoracic and abdominal organs or of the nervous system. The secondary sex-characters were quite well developed and menstruation was regular. There were no abnormal constituents present in the urine. The Wassermann reaction was negative.

X-ray films of the skeleton showed very marked generalized deficiency in density, and the trabeculation was more prominent than normal. There was no cystic formation. The cortices of the long bones were extremely

thin. There was no splaying of the epiphyseal ends or abnormal bowing of the long bones. The pelvis showed marked deformation. The hips were approximated, due to apparent softening of the rami of both pubic bones. These rami were bent to form a beak, and appeared on the verge of fracture. Apart from an accidentally-discovered fractured metatarsal, there was no other evidence of bone fragility.

*Experimental.* Following the clinical investigation, the patient was transferred to the wards of the Biochemical Department, where she was subjected to several experiments.

The basal diet consisted of 85 grm. bread, 55 grm. fresh butter, 20 grm. sugar, 850 c.c. raw milk, 60 grm. potato, 60 grm. cabbage, 103 grm. fish, 40 grm. chicken, 200 c.c. chicken soup, 110 grm. tomato, and one orange, daily. This diet had a  $\text{CaO}:\text{P}_2\text{O}_5$  ratio of 0.75 (Ca:P, 1.9). After five days on this diet, a balance experiment of eleven days' duration was carried through, the faeces being marked off with carmine. The analytical methods employed were similar to those generally used by one of us (Cuthbertson (1930)). The data from this experiment are contained in Tables I and II (*q.v.*). The daily values have not been expressed per kg. body-weight, as all these patients were approximately of the same weight.

The daily intake was then increased by the addition of 1000 c.c. milk. After seventeen days of this additional food, a further balance period of eight days was carried through. Irradiated ergosterol in the form of 'Radiostol' (British Drug Houses, Ltd.), two pellets three times a day, was then exhibited on a dietary similar to that fed during the second period. Each pellet was supposed to contain 6,000 antirachitic rat units, equivalent to considerably more than 6,000 international units—the recent assay unit given by the B.P. 1932. After a pre-period of nine days, a balance experiment of nine days was carried through (Table I, Diet 3).

The patient's blood was examined for calcium and phosphorus in the post-absorptive stage during each of these periods.

The body-weight at the commencement of the first experiment (9.7.32) was 35.4 kg., at the start of the second experiment 36.8 kg., and during the middle of the third balance experiment (27.8.32) 39.0 kg. On 25.1.33 her weight was 42.3 kg.

### Discussion

The outstanding feature in this case is the amazing capacity for the absorption and retention of calcium and phosphorus exhibited. Increased intake of these elements led to increased retention. This retention relative to intake was equal to the capacity of a breast-fed child. Blauberg (1900) gave the value for the retention of calcium by the breast-fed child as 65 per cent.; Holt, Courtney, and Fales (1920) found 66.7 per cent. Of the phosphorus ingested by the breast-fed baby, Keller (1900) found 54 per cent. was retained, provided the milk-supply was adequate. If the latter is poor, the percentage retentions are naturally much higher. The high retention values observed in this first case cannot be attributed to a low intake magnifying their significance, for the basal diet was adequate for the normal subject.

TABLE I (Case I)  
Daily Mineral Exchange During Three Metabolic Periods in Grams

Diet.	Mineral oxides.	Urine.	Faeces.	Total output.	Intake.	Balance.	Percentage retention.	Weight, kg.	Blood analyses, mg. per 100 c.c.	
									Ca. (Serum.)	Inorg. P. (Whole blood.)
1. Ordinary.	CaO	0.22	0.42	0.64	1.77	+1.13	64			
	P <sub>2</sub> O <sub>5</sub>	1.35	0.595	1.945	2.85	+0.905	32	35.4	9.6	3.3
	MgO	0.122	0.181	0.303	0.300	-0.003	-1			
2. Ordinary + 1,000 c.c. milk extra.	CaO	0.235	0.595	0.83	3.43	+2.60	76			
	P <sub>2</sub> O <sub>5</sub>	1.73	0.69	2.42	4.91	+2.49	51	36.8	9.3	3.1
	MgO	0.1265	0.323	0.4495	0.542	+0.093	17			
3. Ordinary + 1,000 c.c. milk + irradiated ergosterol.	CaO	0.28	0.48	0.76	3.47	+2.71	78			
	P <sub>2</sub> O <sub>5</sub>	1.805	0.41	2.215	4.93	+2.715	55	39.0	9.8	3.6
	MgO	0.154	0.240	0.394	0.542	+0.148	27			

TABLE II (Case I)

Diet.	Calcium.		Phosphorus.		Magnesium.	
	Per cent. of total excretion.	Per cent. of intake.	Per cent. of total excretion.	Per cent. of intake.	Per cent. of total excretion.	Per cent. of intake.
Urinary excretion.	1 34	12	69	47	40	41
	2 28	7	71	35	28	23
	3 37	8	81	37	39	19
Faecal excretion.	1 66	24	31	21	60	60
	2 72	17	29	14	72	60
	3 63	14	19	8	61	44

It will be noted that an increase of 93 per cent. in the intake of lime caused but little change in the distribution of the calcium excreted, even although the percentage retention rose to a still higher level. Such a change in the distribution as occurred resulted in relatively more being excreted by the bowel than in the urine. The effect of the added irradiated ergosterol was to reverse this slight change.

An increase of about 72 per cent. in the intake of phosphorus led to practically no alteration in the distribution between urine and faeces; the percentage retention increased to the same extent as the calcium. The administration of irradiated ergosterol caused relatively more phosphorus to appear in the urine than in the faeces.

It is of interest that, despite these great retentions of calcium and phosphorus, the levels of these constituents in the blood did not vary to any marked extent.

The 80 per cent. increment in the magnesium intake produced somewhat similar but more pronounced changes in the distribution of the excreted magnesium than had been noted in the case of calcium. Again, the effect of the irradiated ergosterol was to reverse this change.

While the general effect of the addition of irradiated ergosterol was to increase the percentage retention of all three elements slightly, this increment was as nothing when compared with the increased retention which resulted from the addition of a litre of milk daily.

The retention capacity of this subject is also evident from her gain of 3.6 kg. in the space of forty-eight days during these metabolic experiments, and by the increment to date of 6.9 kg.

If it be assumed that 25 per cent. of the retained phosphorus is assimilated into tissues other than bone, then the average  $\text{CaO}:\text{P}_2\text{O}_5$  ratio of the retained material during these experiments would be 4.1:1, a ratio comparing closely with that of 4.7:1 found for bone by McCrudden (1910). The level of calcium and phosphorus in the blood was maintained within normal limits throughout the period of observation.

Since the basal diet cannot be considered entirely devoid of vitamin D, fresh butter and raw milk during the summer months being sources of this dietary substance, we cannot definitely ascribe the increased improvement in this patient's skeletal system solely to the mineral adequacy of her experimental diet, though it is our conjecture that this was the case. Milk cannot be regarded as a rich source of vitamin D, Coward (1929) and Burn (1930). Crawford, Golding, Perry, and Zilva (1930) have shown that the vitamin D content of milk is associated with the fat. In our cases fresh butter was consumed in ordinary amount, and was thus probably the main available source of this vitamin. In the cases still to be described, the basal diets did not produce marked retentions, despite the fact that the amount of fresh butter consumed was not substantially different from that consumed in this first case.

It was apparent from the patient's previous dietary history that her

skeleton had been mainly starved, although her total caloric intake was also probably inadequate for her requirements. This mineral starvation is evident from the defective calcification observed on the X-ray films, and the reaction to treatment indicated by the general increase in the density of the bones and the definite increase in cortical thickness. While the X-ray picture resembled that seen in osteogenesis imperfecta, there was no history of any of the usual conditions associated with that defect—namely, blue sclerotics, fragilitas ossium, otosclerosis, and hyperlaxity of joint ligaments; nor was there any familial history of such inherited abnormalities. Further, the reaction to diet was quite different from the balanced intake and output generally observed in that condition (Stevenson and Cuthbertson (1931)).

From all aspects it seems most appropriate to consider this nutritional defect as allied to the 'war osteopathy' which appeared in Central Europe just after the World War, and which showed a high incidence in adolescents and in those between forty and sixty years (Beninde, 1930).

*Case 2. Juvenile, now late, rickets.*<sup>2</sup> I. R., female, aged 20 years, was admitted to Glasgow Royal Infirmary (18.12.28), complaining of continuous deep gnawing lumbar and pelvic pain, inability to stand and difficulty even in sitting up in bed.

*Present illness.* About the age of 13 years the patient began to experience difficulty in performing gymnastics at school owing to occasional pain and weakness of her right leg, chiefly in the region of the knee-joint. At this time her diet consisted of bread, salt butter, gravy or meat, oranges, tea, cocoa, and sometimes half a cupful of milk daily. A year later a definite genu valgum developed. She consulted the late Sir William Macewen, who performed the operation of osteotomy. A year after the operation she began to suffer from a deep gnawing lumbar pain, at first intermittent, latterly continuous. At the age of 16½ years she could neither walk nor stand, and she could only sit up in bed with difficulty.

*Previous health.* As a baby she was bottle-fed. At the age of 15 months she was walking, and up to the age of 12 years she was to all appearances a healthy active child.

*Family history.* There was nothing of note in the family history, the patient being the only member thus affected in a family of nine children.

*Condition on admission.* A pale, undersized, but apparently plump, dark-haired woman; 41.2 kg. in weight, and 129 cm. in height. As in the previous case there was no unusual blueness of the sclerotics. The teeth and gums were in good condition. A line of early defective tooth formation was evident, but the more recently formed zone was apparently normally developed. There was some bossing of the head, and a rachitic rosary and a Harrison's sulcus were present.

The spine showed a considerable degree of scoliosis in the lumbar region, and the degree of genu valgum had apparently increased recently. The soft parts were relatively well developed, particularly in the abdominal and pelvic regions. This degree of fat deposition did not amount to a dystrophy, nor was it the concomitant of a chondrodysplasia. The degree of scoliosis

<sup>2</sup> Brief references to the metabolism of this case and also that of Case 5 were made in an earlier paper, Cuthbertson (1930). The cases are now fully described.

TABLE III (Case 2)  
Average Daily Mineral Exchange During Five Metabolic Periods in gm.

Diet.	Calcium and phos- phorus.	Urine.	Faeces.	Total output.	Intake.	Balance.	Percentage retention.	Blood analysis mg. per 100 c.c.		Faecal fat (per cent. in dry matter).	
								Ca.	P.	Neutral.	Fatty acids (free and combined as soaps).
1. Ordinary.	CaO	0.18	0.76	0.94	1.01	+ 0.067	6.6	10.1	1.6	5.46	8.32
	P <sub>2</sub> O <sub>5</sub>	0.64	0.97	1.61	1.61	0.000	Nil.				
2. Ordinary + calcium glycero-phosphate.	CaO	0.16	1.58	1.74	1.005 +	+ 0.285	14				
	P <sub>2</sub> O <sub>5</sub>	—	—	—	1.02 1.61 + 1.29	—	—	—	—	7.86	8.49
3. Ordinary + calcium glycero-phosphate + ir- radiated ergosterol.	CaO	0.30	0.65	0.95	1.06 +	+ 1.75	65				
	P <sub>2</sub> O <sub>5</sub>	1.48	0.57	2.05	1.64 1.77 + 2.08	+ 1.80	47	—	—	—	—
4. Ordinary + phytin + irradiated ergosterol.	CaO	0.26	0.89	1.15	1.06 +	+ 1.03	47				
	P <sub>2</sub> O <sub>5</sub>	1.71	1.74	3.45	1.12 1.77 + 3.36	+ 1.68	33	—	—	—	—
5. Ordinary + cal. and sod. lactates + irradi- ated ergosterol.	CaO	0.25	0.28	0.53	1.06 +	+ 0.68	56	9.35	1.7	1.3	10.90
	P <sub>2</sub> O <sub>5</sub>	0.96	0.32	1.28	0.15 1.77	+ 0.49	28				

probably accentuated this effect. The secondary sex characters were well developed. There was no marked disproportion of the limbs, though the legs appeared to be somewhat shorter than normal.

No apparent abnormality of the thoracic and abdominal organs existed. There was a marked tendency to constipation. The nervous system was normal. There were no abnormal constituents in the urine, and the Wassermann reaction was negative.

The X ray films showed a general deficiency in bone density, and the trabeculation was coarse and wide-meshed. The cortices were extremely thin, and the long bones, with the exception of the humeri, were bowed. There were lines of arrested growth in the distal ends of the long bones. The remaining ununited epiphyses of the iliac bones were poorly formed and frayed. The epiphyseal ends of the long bones, the femora in particular, were splayed.

TABLE IV (*Case 2*)

	Diet.	Calcium.		Phosphorus.	
		Per cent. of total excretion.	Per cent. of intake.	Per cent. of total excretion.	Per cent. of intake.
Urinary excretion.	1	19	18	40	39
	2	9	8	—	—
	3	32	11	72	38
	4	23	12	50	33
	5	47	21	75	54
Faecal excretion.	1	81	75	60	60
	2	91	78	—	—
	3	68	24	28	15
	4	77	40	50	34
	5	53	23	25	18

*Experimental.* In point of time the investigations on this case and on the next three preceded the first case by a period of one to three years. It is more convenient to describe them in the reverse order. These metabolic investigations, while based on the same general principles—namely, the measurement of the effect of first, ordinary diet, then ordinary diet plus additional mineral matter, and finally, the effect of the superimposition of irradiated ergosterol, are not similar in all respects. Owing to the initial difficulty in persuading this patient (I. R.) to consume a diet of adequate proportions, a much lower basal diet had to be accepted. The only method by which she could be made to take milk was in dry form. Subsequently some was taken in solution. This lack of appetite persisted.

The basal diet consisted daily of 140 gm. brown bread, 40 gm. fresh butter, 30 gm. wheaten biscuit, 'Cow and Gate' half-cream dried milk contributing 0.867 gm. CaO and 1.035 gm.  $P_2O_5$ , and orange juice. The CaO :  $P_2O_5$  ratio of the diet was 0.63 ; as Ca : P, 1.03.

Ten days after the commencement of this diet the first metabolic period was held and lasted four days. The data are presented in Tables III and IV (*q.v.*).

Following these observations calcium glycerophosphate was added to the diet as a further source of calcium, since the patient refused to take more milk. This substance was administered on five days during a twelve-day period, 10 gm. per day being consumed with food. The amount used approximately doubled the intake of calcium and phosphorus.

Seventeen days after the close of this second experiment, the patient was

given irradiated ergosterol in the same form as that administered to the first case (two pellets, three times a day with food). Seven days after the commencement of this therapy, a third balance experiment was made over a six-day period, the basal diet containing added calcium glycerophosphate (40 grm. spread over four days).

In the next balance experiment of six days 40 grm. phytin, also in 10 grm. doses, was administered in place of the glycerophosphate.

In the last six-day experiment of this series, calcium and sodium lactates were exhibited in place of the phytin (20 grm. 'Kalzana'—5 grm. daily).

The patient's blood was examined in respect of the levels of calcium and phosphorus at the beginning and end of these experiments.

On 18.2.29 her weight was 42.1 kg.; one week later 41.4 kg. After treatment with vitamin D, her weight rose to 42.2 kg. by 18.3.29. Subsequent to her dismissal from hospital she lost weight. On 12.2.30 her weight was 39.6 kg., on 13.3.33, 32.8 kg. This loss of weight can be attributed to the low intake of food she chose when not under hospital supervision.

### *Discussion*

In marked contrast to the first case this patient was practically in equilibrium in respect of calcium and phosphorus on the basal diet provided. Further, the plasma phosphorus was distinctly below normal. The distribution and amount of the fatty substances in the faeces revealed no obvious deviation from normal. (The fatty acids were calculated as stearic). No sufficient reason for this patient's defective appetite has as yet been ascertained.

The calcium in the urine represented 19 per cent. of the total excretion, and the phosphorus 40 per cent., values considerably lower than those found in the first case. Doubling the intake of calcium and phosphorus by means of calcium glycerophosphate caused but little change in the degree of calcium retention. The exhibition of irradiated ergosterol, however, produced a dramatic change: the retention of calcium rose to 65 per cent., and that of phosphorus to 47 per cent. This retention contrasts with the relatively slight change produced by irradiated ergosterol in the first case. As a result of this therapy an increase in the relative amounts of calcium and phosphorus excreted in the urine took place coupled with an absolute decrease in the faecal excretion of these substances.

The retentions of calcium and phosphorus when phytin was used as the source of extra mineral matter amounted to 47 per cent. and 33 per cent. respectively. The relative amounts of calcium and phosphorus excreted in the urine were somewhat less than in the case of the glycerophosphate.

The marked retention of calcium and phosphorus was maintained in the final period when sodium and calcium lactates were administered. The amount of extra calcium ingested in the form of lactate was slight, amounting to an increase of only 14 per cent. The administration of these lactates ('Kalzana') increased to the greatest extent the relative amount of calcium and phosphorus excreted in the urine. The level of the plasma phosphorus remained subnormal despite irradiated ergosterol therapy.

From the clinical and metabolic standpoint this patient would appear to have been originally a case of juvenile rickets, now late rickets, with persistently low blood phosphorus. The cause of the chronic undernutrition was the extreme lack of appetite of unknown origin, being unaccompanied by any obvious gastric derangement as judged by radiological and fractional test-meal examinations.

The clinical improvement was very marked. After having been completely bedridden for over a year prior to admission to hospital, she was dismissed walking unaided and able to do light housework.

*Case 3. Juvenile rickets.* It is of interest to compare the metabolic response exhibited by this last case and that found in a somewhat similar late rachitic condition occurring in a youth (W. W.) aged 15 years. As in the former case this patient's condition appeared to be due to idiosyncrasies in diet, and not economic circumstances, leading to defective nutrition.

*Present illness.* Until he was four years of age the patient was in good health and had regular courses of cod liver oil. He went to school at the age of five years and about that time commenced to have dislikes for certain foodstuffs because he thought they made him 'sick'. His dietary from that date until he came under our hospital supervision consisted of fruit, potatoes, bread, and a very little butter and milk (about half a pint daily). Meat, fish, eggs, puddings of all descriptions, porridge, and soups were excluded.

At the age of thirteen years an osteotomy had to be performed on the right leg; a year later the left femur had to be similarly treated.

*Family history.* He is the only member of a family of eight children thus affected.

*Condition on admission (9.4.30).* A dark-haired, moderately well-nourished, boy of 15 years, 132 cm. in height and weighing 40 kg.

There was no evidence of frontal bossing, beading of the ribs, thoracic sulcus, or scoliosis. There was no laxity of the joint ligaments nor history of bone fragility. While the legs appeared shorter than normal, due mainly to the deformities, there was no disproportion between the arms and the trunk.

The X-ray films showed generalized defective calcification and thinning of the cortices. The pattern of the long bones, particularly at their distal and proximal ends, was of loose and irregular texture. On the shafts of the bones of the lower leg were numerous transverse lines and the epiphyseal lines which remained were frayed. There was a considerable degree of coxa valga and the distal end of the right femur was splayed. The femora were bowed outwards and the bones of the right leg were bowed to the left.

### *Experimental*

On a basal daily dietary of 430 c.c. raw milk, 100 gm. brown bread, 45 gm. fresh butter, 60 gm. wheaten biscuit, sugar and fruit, the percentage retention of calcium was 9.

Following the first metabolic period on this diet irradiated ergosterol was administered, and after the lapse of ten days on this therapy another

balance experiment was held. It is obvious that the administration of this therapeutic agent accelerated the rate of calcium deposition, the percentage retention rising from 9 to 68. This retention was due to a decrease in the faecal output.

TABLE V (Case 3)

*Daily Calcium Exchange During Three Metabolic Periods in grm.*

Diet.	Urine.	Faeces.	Total.	Intake.	Balance.	Percentage retention.	Faecal fat (per cent. dry matter.)	
							Neutral.	Fatty acids free and combined as soaps.
Ordinary	0.03	1.17	1.20	1.325	0.125	9	3.04	7.56
Ordinary + irradiated ergosterol.	0.02	0.42	0.44	1.38	0.94	68	—	—

TABLE VI (Case 3). Calcium

	Diet.	Per cent. of total excretion.	Per cent. of total intake.
Urinary excretion.	1	2.5	2.0
	2	4.5	1.5
Faecal excretion	1	97.5	88
	2	95	30

The urinary excretion of calcium was very low—2.5 per cent. of the total—only about a tenth of that of the other cases. There was no evidence of any renal defect. The non-protein and urea nitrogen contents of the blood were 33 and 14 mg. per 100 c.c. respectively. The faeces were normal in appearance and there was no abnormal amount or partition of fat.

While the blood of the previous case showed a low inorganic phosphorus and normal serum calcium content both before and after treatment, this case showed a normal phosphorus content (4.5 mg. per 100 c.c.) and a relatively low serum calcium (9.1 mg. per 100 c.c.) when examined a few days after administration of irradiated ergosterol had commenced.

On dismissal from hospital after two months' treatment the patient was considerably improved. Unfortunately he resumed his old dietary habits and relapsed. A stern reprimand had a salutary effect, and he now takes an adequate dietary with the addition of irradiated ergosterol in winter. He is now greatly improved. The inorganic phosphorus and urea-nitrogen contents of the whole blood are now (13.3.33) 2.22 mg. and 13 mg. per 100 c.c. respectively, but the serum calcium is only 8.6 mg. per cent. It would appear that the end results in the last two cases justify their inclusion in the group of late rickets.

In relation to the essentially vegetarian diet of Case 3 it is of interest to note that Schultzer (1933) has described a case of 'osteomalacia' occurring in a patient aged 55 years, who had been a vegetarian for twenty-one years. Treatment with vitamin D and calcium chloride resulted in marked improvement.

*Case 4. Chondrodystrophy with superimposed juvenile rickets. Present illness.* At the age of 3 years the patient (G. McK.) was found to be unable to walk, and during childhood deformities of the limbs gradually developed. At the age of twelve she was admitted to the Royal Hospital for Sick Children, Glasgow, where three osteotomies were performed—right and left tibiae and right femur. Thereafter she attended a special school where her condition was the subject of investigation by the School Medical Authority of Glasgow, and in May 1931 she was admitted to Meanskirk Hospital as a case of severe rickets. To improve the deformities a double osteotomy of the left femur and tibia was carried out. At the operation Mr. Dale found the femur to be relatively hard, but the cortex of the tibia was no thicker than parchment and caved in before the osteotome. When this was penetrated a thin gelatinous substance exuded. Healing was slow, and three months later she was transferred to this hospital for biochemical investigation.

*Family history.* Nothing of note.

*Condition on admission.* An undersized, disproportioned, fat girl of 16 years, 100 cm. in height and 28.6 kg. in weight.

The head was large and square, the frontal regions protruding slightly. The root of the nose was not sunken. The hair was dark and coarse. The hands and feet were small, the former trident-like; the limbs were very short and stumpy and the skin lay in folds on the thighs. The umbilicus represented the mid point of the body.

There were considerable deformities present—scoliosis, genu valgum, and slight anterior curving of the femora and bones of the legs. The patient was 'pot-bellied', and there was some evidence of beading of the ribs. The heart and lungs were normal. The urine was free of abnormal constituents and the Wassermann reaction was negative.

The X-ray films showed:

*Skull.* Protruding frontal region with the bone thinnest at that part.

*Thorax.* Somewhat conical in shape.

*Pelvis.* Somewhat flattened by pressure from the heads of the femora. The blades of the ilea mottled and their outlines ill-defined. Obvious defective calcification. Sacrum scarcely visible and the vertebrae ill-defined.

*Lower limbs.* Coarse and irregular trabeculation of the heads and necks of the femora. Marked bowing and coxa vara of the femora, the lower ends showing a coarse pattern; splaying of the left condylar region.

Epiphyseal lines of upper ends of the tibiae very thin and broken and adjacent areas of epiphyses and diaphyses of loose texture. Numerous transverse lines on the shafts and evidence of old osteotomies. Lower ends of fibulae enlarged, and with the lower ends of tibiae formed cup-shaped hollows for the calcanei. Corticales of femora, but more particularly those of bones of the legs, very thin.

*Upper limbs.* Humeri and forearm bones short and thick. Distal epiphyseal ends of the bones of forearm very frayed and of coarse pattern, no defined line being apparent. Metacarpals and phalanges short and stubby.

*Experimental.* Following the clinical investigations the patient was put on a basal diet of 640 c.c. raw milk, 215 gm. brown bread, 70 gm. fresh butter, 25 gm. egg, 150 gm. beef steak, 40 gm. tomato, 90 gm. wheaten biscuit, one orange, and one apple. Four days later the first metabolic

period was held (eight days' duration). Irradiated ergosterol was then administered (three 'Radiostol' pellets daily) and a month later another balance experiment of eight days conducted. The patient then received an extra litre of milk daily. Four days later a final balance period of eight days was held.

TABLE VII (Case 4)

*Average Daily Calcium Exchange During Three Metabolic Periods*

Diet.	Oxides.	Urine.	Faeces.	Total output.	Intake.	Balance.	Percentage retention.	Blood analyses.	
								Serum Ca.	Plasma inorg P.
1. Ordinary diet.	CaO	0.18	1.17	1.35	1.35	0.00	0	10.8	2.2
	P <sub>2</sub> O <sub>5</sub>	1.88	1.01	2.89	3.17	+ 0.28	9		
	MgO	0.203	0.313	0.516	0.555	+ 0.039	7		
2. Ordinary diet + irradiated ergosterol.	CaO	0.16	0.85	1.01	1.39	+ 0.38	27	12.7	1.9
	MgO	0.217	0.228	0.445	0.555	+ 0.110	20		
3. Ordinary diet + 1,000 c.c. milk extra + irradiated ergosterol.	CaO	0.13	1.52	1.65	3.05	+ 1.40	46		
	P <sub>2</sub> O <sub>5</sub>	2.135	1.16	3.295	5.25	+ 1.955	37		
	MgO	0.193	0.252	0.445	0.797	+ 0.352	44		

TABLE VIII (Case 4)

Diet.	Calcium.		Phosphorus.		Magnesium.	
	Per cent. of total excretion.	Per cent. of intake.	Per cent. of total excretion.	Per cent. of intake.	Per cent. of total excretion.	Per cent. of intake.
Urinary excretion.	1	13	13	65	40	37
	2	15	12	—	49	39
	3	8	4	65	44	25
Faecal excretion.	1	87	87	35	60	56
	2	85	61	—	51	41
	3	92	50	35	66	32

*Discussion*

On ordinary diet the intake and output of calcium balanced. There were small retentions of phosphorus and magnesium indicating anabolism of soft tissues. The serum calcium of the blood was 10.8 mg. per 100 c.c., and the plasma phosphorus 2.2 mg. per 100 c.c. On adding irradiated ergosterol to this diet a definite retention of calcium rapidly took place amounting to 27 per cent. of the intake during an eight-day period held four days after the administration of this substance. Subsequently the capacity for retention increased, and when the intake of mineral matter was practically doubled by the addition of an extra 1000 c.c. of milk daily, retentions of 46, 37, and 44 per cent. of the respective intakes of calcium, phosphorus, and magnesium were noted.

It will be seen from Tables VII and VIII that the effect of the irradiated ergosterol was to cause a definite decrease in the faecal excretions of the various minerals.

In October 1931 the patient's weight was 28.6 kg.; in March 1933, 45.2 kg.

From the clinical evidence it would appear that this patient was primarily a case of chondrodystrophy, and that superimposed on that condition was a later rachitic element obvious in the X-ray films of the wrist-joint and substantiated by the great improvement in the patient's condition which followed the administration of irradiated ergosterol. On dismissal the patient was able to walk out of the hospital unaided.

*Case 5. Late rickets (osteomalacia).* J. W., a female, aged 31 years, was admitted to Glasgow Royal Infirmary (3.3.28) complaining of aching pain in her left groin which radiated round to her back.

*Present illness.* Seven weeks after the birth of her fifth and last child (28.10.23) the patient while out walking one day suddenly felt great pain in her left groin. She had to be carried home. After four and a half months in bed she was able to get up, but now walked with a rocking movement and had to be supported with two sticks. She gradually gained strength and confidence, but still had a 'wobbly' gait. Two years later an occurrence of exactly the same nature again took place in the street. Sudden severe pain was experienced in the same region. After four months she was able to get about very slowly and with the aid of two sticks. Latterly such slight improvement as had occurred seemed to be dwindling and she was admitted to hospital in January 1927. There was no history of tetanic manifestations.

*Previous health.* Apart from chronic bilateral middle ear suppuration dating from an attack of measles in childhood the patient had suffered no serious illness. An inquiry into the patient's dietary habits revealed that up to the age of 19 years her diet lacked butter (dripping from roast meat being used as a substitute) and sufficient milk. During the first seven years of her married life she only took butter occasionally, generally during her pregnant periods, margarine being the main source of fat. Whole milk was never consumed, but during her pregnancies she often drank one or two pints of buttermilk daily. Butter fat was supposed to make her 'bilious'. Straitened circumstances were not a primary factor in this malnutrition.

The births of her first and second children were difficult, instruments having to be used. The births of the subsequent three children were normal.

*Family history.* There was no noteworthy feature.

*Present condition.* A fair-haired, undersized, but relatively well-nourished woman, 42 kg. in weight and 138 cm. in height.

The patient's sclerotics were somewhat bluish and there was some hyperlaxity of the joints of her stubby fingers. She was not anaemic and her teeth were in fairly good condition. The heart and lungs were normal. There was no evidence of beading of the ribs or of sulcus formation nor any signs of tetany. The limbs were not abnormal in length. Apart from some lordosis and genu valgum, there was no marked abnormality of the skeleton visible externally. She was unable to put her feet to the ground without help; even rising in bed was difficult. There was a systolic murmur heard over the praecordium. The lungs and nervous system were normal. There were no abnormal constituents found in the urine. The Wassermann reaction was positive, but there were no signs of specific disease.

The menstrual periods were regular, but the loss of blood was profuse. The intercrystal diameter of the pelvis was 23 cm., the interspinous 18.7 cm., and the external conjugate 19.4 cm. (largely on account of the obliquity). The diagonal conjugate could not be measured as it was impossible to reach the promontory on account of the narrow angle between the pubic bones. The transverse diameter at the outlet was 3.75 cm.

TABLE IX (*Case 5*)*Average Daily Calcium Exchange During Three Metabolic Periods*

Diet.	Oxides.	Urine.	Faeces.	Total output.	Intake.	Balance.	Percentage retention.
Ordinary.	CaO	0.38	1.36	1.74	1.82	+0.08	4
	P <sub>2</sub> O <sub>5</sub>	1.66	1.17	2.83	2.75	-0.08	-3
Ordinary + irradiated ergosterol (2 months' treatment).	CaO	0.29	1.15	1.44	1.95	+0.51	26
Ordinary + irradiated ergosterol (17 months' treatment).	CaO	0.35	0.71	1.06	1.72	+0.66	38
	P <sub>2</sub> O <sub>5</sub>	1.34	0.57	1.91	2.48	+0.57	23

TABLE X (*Case 5*)

Diet.		Calcium.		Phosphorus.	
		Per cent. of total excretion.	Per cent. of intake.	Per cent. of total excretion.	Per cent. of intake.
Urinary excretion.	1	22	21	58	60
	2	20	15	—	—
	3	33	20	70	54
Faecal excretion.	1	78	74	42	43
	2	80	59	—	—
	3	67	41	30	23

The X-ray films showed that there had been a fracture of the superior and inferior rami of both pubic bones; there was evidence of fibrous healing with a resulting 'beaked' pelvis. There were ill-defined areas of rarefaction in the blades of the ilea producing a somewhat moth-eaten appearance. The pelvis, sacrum, spine, and ribs were particularly affected by this process of osteoporosis. The long bones showed marked thinning of the corticales. There was also more marked rarefaction at the distal ends of the femora and the proximal ends of the bones of the legs. The left femur had a small cyst-like area at its distal end and also another near the lesser trochanter. There were cyst-like areas in the bodies of the metacarpals and phalanges generally near the heads; these did not expand the bone. The distal ends of the bones of the arms were more rarefied than the rest of the shafts, and there were a few small ill-defined cyst-like areas at the distal ends of the bones of the left forearm. Pressure over the long bones elicited no hyper-sensitiveness.

The calvaria showed numerous round 'moth-eaten' areas about the size of sixpenny pieces. The appearances of the skeleton were very similar to the radiograms of a case of osteomalacia shown by Hunter (1931).

Unfortunately the calcium and phosphorus levels of the blood were not determined on admission. Five months after the cessation of vitamin D therapy the levels were: serum calcium 10.7 mg., plasma phosphorus 3.0 mg.

*Experimental.* On admission to the metabolic wards the patient was put on a basal daily diet of 100 gm. dried milk, 34 gm. wheaten biscuit, 20 gm oatmeal, 28 gm. brown bread, 7 gm. tapioca, 25 gm. dried soup powders, 30 gm. fresh butter, 4 gm. egg powder, and fresh fruit. The dried products were consumed in a dissolved or suspended form. After a pre-period of four days on a constant diet a balance period of seven days was held. Irradiated ergosterol as 'Radiostol' (two pellets twice daily) was given. After two months' treatment another balance experiment was carried through, and then seventeen months after the commencement of treatment a final period was held. The diet remained practically constant throughout these periods. The  $\text{CaO}:\text{P}_2\text{O}_5$  ratio of the diet was 0.66; as  $\text{Ca}:\text{P}$ , 1.09.

The patient made a fairly satisfactory recovery, being able to resume most of her household duties two months after dismissal. At periodic intervals her condition was examined. Subsequently she lapsed into her earlier deficient dietary habits. On readmission to hospital she rapidly gained weight on suitable diet and irradiated ergosterol. The patient is now (13.7.33) greatly improved. The plasma inorganic phosphorus is 1.6 mg., the serum calcium 11.3 mg. per 100 c.c.

#### *Discussion*

The clinical and biochemical findings appear to indicate that this case is an example of late rickets (osteomalacia) rather than a case of osteitis fibrosa cystica, being due primarily to vitamin D deficiency caused by faulty dietary habits and the drain of successive pregnancies.

On ordinary diets the percentage retentions of calcium and phosphorus were +4 per cent. and -3 per cent. respectively. After two months' administration of irradiated ergosterol the retention of calcium was 26 per cent. of the intake, while after seventeen months' therapy the percentage retentions of calcium and phosphorus were 38 and 23 respectively. There was thus a definite increased retention and clinical improvement due to the exhibition of irradiated ergosterol.

It will be noted that the main effect of giving vitamin D was a progressive decrease in the faecal excretion of calcium and phosphorus, a phenomenon common to all cases reacting favourably to vitamin D therapy.

#### *Concluding Remarks*

While it is possible that some difference in the degree of absorption of the mineral matter on the different basal diets of these cases may be attributed to differences in the relative assimilability of these substances as found in raw and dried milk, such variations in character could not account for the enormous initial differences in the capacity for retention exhibited by Case 1 as compared with Cases 2 and 5, since these cases and also Cases 3 and 4

who received raw milk, did not show any marked retention capacity until irradiated ergosterol was added to their diets.

It is improbable that differences in the vitamin D content of these two kinds of milk would account for these differences in retention, for the effect of the administration of irradiated ergosterol in Cases 2 and 5 who received dried milk, and Cases 3 and 4 who received raw milk, indicated that high retentions were not possible in these cases until the deficient vitamin had been made good.

With regard to the condition termed 'hunger osteopathy' or 'hunger osteomalacia' some doubt exists as to its true nature. Both Partsch (1919) and Schmorl (1920) regard the histological lesions as those of true osteomalacia and not as a new nutritional disorder. They point out that there is an extreme osteoporosis. Dalyell and Chick (1921) and Hume and Nirenstein (1921) found that, for a large series of cases occurring in Vienna, cod liver oil was a specific remedy. From an examination of these Viennese case records it appears possible that the patients were mainly cases of late rickets (osteomalacia).

Loll (1923) has noted in his analysis of the bones in hunger osteopathy that in addition to the general decrease in ash there is a relative increase of calcium and decrease of phosphorus, a significant contrast to the normal ratio found in rickets (Hess, 1930), and the relative decrease in calcium over phosphorus observed by McCrudden (1910) in the bones of a case of late rickets (true osteomalacia).

If our interpretation of our clinical and metabolic findings is correct then our data would suggest that hunger osteopathy and late rickets (osteomalacia) are not necessarily identical in their defective nutritional origin. It would appear more appropriate to consider late rickets (osteomalacia) as one particular type of hunger osteopathy—namely, that primarily due to vitamin D deficiency, since there are many hygienic deficiencies which affect the development and maintenance of such an active metabolic tissue as bone, each producing its peculiar effect. It is of some interest that the pathological condition of at least three of these five cases appeared to be primarily due to individual perversity and not to economic circumstances.

#### *Summary*

1. The clinical and metabolic findings in a case of hunger osteopathy, two cases of juvenile rickets, one case of chondrodystrophy associated with rickets, and a case of late rickets (osteomalacia) have been described.

2. The essential difference between the metabolism of the case of hunger osteopathy and the rachitic conditions lay in the fact that the former rapidly stored calcium, phosphorus, and magnesium without the addition of irradiated ergosterol, increased intake of mineral matter leading to increased retention; while on the other hand the rachitic cases only showed a noteworthy retention of mineral matter when irradiated ergosterol was added to the diets.

3. It is considered that hunger osteopathy and late rickets (osteomalacia) are not necessarily identical in their nutritional origin, but that late rickets (osteomalacia) is a form of hunger osteopathy, namely, that due to deficient vitamin D.

In conclusion we wish to express our thanks to Prof. Hendry, Mr. John Patrick, Mr. James Taylor, and Dr. Fleming for allowing us access to their patients, and to Sister Cumming for her supervision of the metabolism experiments.

We are indebted to the British Drug Houses Ltd. for a supply of 'Radiostol'.

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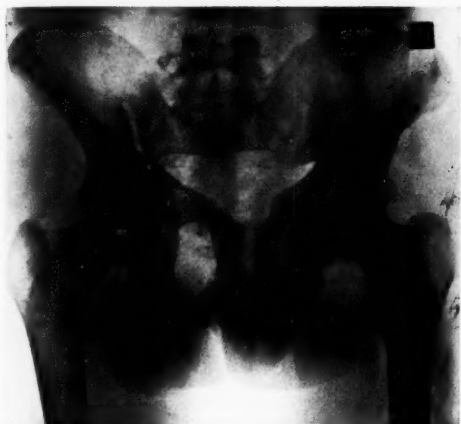


FIG. 1. Case 1. On admission



FIG. 2. Case 1. Present condition



FIG. 3. Case 2. On admission



FIGS. 4 and 5. Case 2. On admission





FIG. 6



FIG. 7



FIG. 8

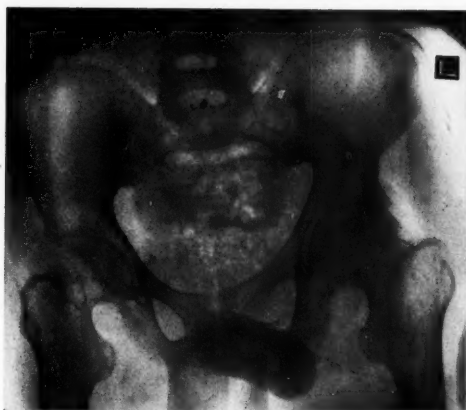


FIG. 9

Case 3. On admission





FIGS. 10 and 11. Case 4. On admission



FIG. 12. Case 4. On admission



FIG. 13. Case 5. On admission

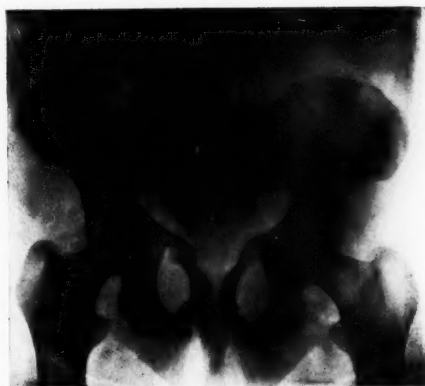
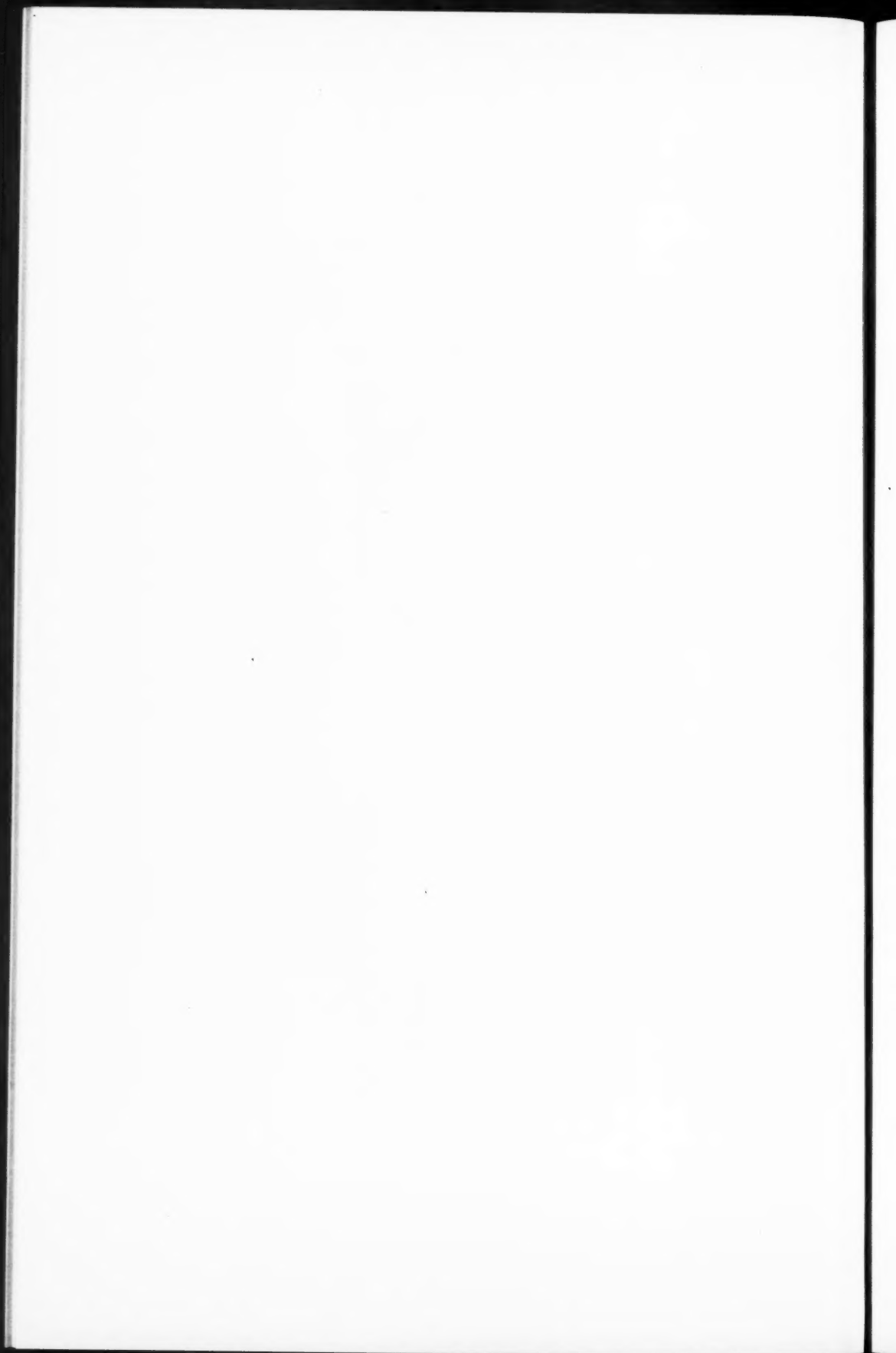


FIG. 14. Case 5. Present condition



## THE PREVENTION AND TREATMENT OF INDIVIDUAL ATTACKS OF ANGINA PECTORIS (ANGINA OF EFFORT)<sup>1</sup>

By WILLIAM EVANS AND CLIFFORD HOYLE

(From the Cardiac Department of the London Hospital)

WHEN dealing with the continuous drug treatment of angina pectoris we (21) showed that of sixteen active drugs none lessened the severity or frequency of attacks. These results emphasized the need for a more general use of vasodilators. Yet, in the choice of these also, we found that there was diversity of opinion; consequently we decided to compare the relative values of those remedies recommended both for the relief of individual attacks and for their immediate prevention.

*Selection of patients.* The investigation has occupied three years and was conducted on patients attending the Cardiac Department of the London Hospital. Our series consists of 122 patients and comprises 90 described in our previous paper on continuous treatment, and 32 additional patients with angina pectoris, in 25 of whom it was due to syphilis. In these last the Wassermann reaction was positive in the blood-serum, arteriosclerosis was not pronounced, and the diagnosis was usually supported by the radiological appearances of the aorta. As with the 90 patients forming our first series, so also in each of the remaining 32, a detailed clinical examination was made and an electrocardiogram taken. Coronary thrombosis was excluded, except when it sometimes happened as a complication. The criteria which admitted a patient into the series as a case of angina pectoris of effort were enumerated in our previous paper and they apply equally to the additional patients in the present series. Most of the patients visited the Department at fortnightly or monthly intervals: many were admitted to hospital for short periods of special observation.

*Drugs used.* The following drugs were tested: glyceryl trinitrate (trinitrin) in tablets, in the 1 per cent. alcoholic solution, in solution in oil, and also as proprietary preparations—natirose dragees (Nativelle), nitrolingual capsules (Pohl), and trinitrine caféinée pills (Dubois); amyl nitrite, sodium nitrite, brandy, chloroform, carminatives, and hypnotics.

It is first necessary to discuss two important questions which were found to decide largely the efficient action of glyceryl trinitrate tablets, namely, their keeping properties on storage, and their absorption.

Glyceryl trinitrate tablets with either chocolate or lactose base were used.

<sup>1</sup> Received November 4, 1933.

They were made by the hospital dispensary or by a manufacturing firm, and each tablet contained 1/100 gr. (0.0006 grm.), 1/50 gr. (0.0012 grm.), 1/25 gr. (0.0024 grm.), or 1/12 gr. (0.005 grm.). We wished to know that the tablets as prepared in bulk actually contained the specified amount of the drug, and also whether they deteriorated when stored. Unequal distribution of the drug in the tablet mass during manufacture, or loss of activity by chemical change or volatilization during storage might each render them inert. There is no evidence bearing upon either of these problems, because no method has been available for the assay of glyceryl trinitrate sufficiently sensitive to estimate accurately the minute quantity present in single tablets. It is true that occasional reference (41, 47) has been made to deterioration of the tablets, but this has been based only upon their therapeutic ineffectiveness.

*Assay of glyceryl trinitrate (trinitrin) tablets.* Mr. C. H. Sykes, Ph.C., (87) Pharmacist to the Hospital, has devised a method of estimating small quantities of glyceryl trinitrate which can be trusted for the assay of single tablets:

The method depends upon the colorimetric comparison of the blue colour produced by the action of diphenylamine on glyceryl trinitrate with a standard obtained by its action on potassium nitrate. Glacial acetic acid is the most satisfactory solvent for the tablets. Each tablet to be assayed is crushed to a fine powder and dissolved in 2.5 c.c. of glacial acetic acid in a small hard glass test-tube fitted with a rubber stopper. Maceration is allowed to occur for two hours, and then 1 c.c. of the solution is withdrawn by pipette and placed in a 10 c.c. graduated test-tube. 0.25 c.c. of a 0.5 per cent. solution of diphenylamine in concentrated sulphuric acid is then added, and the tube suspended in cold water and shaken. After three minutes the tube is removed from the water and glacial acetic acid added to bring the total volume up to 10 c.c. with constant shaking to ensure proper mixing. The standard solutions for comparison are prepared by dissolving 0.0346 grm., 0.0231 grm., and 0.0173 grm., of potassium nitrate in 100 c.c. of glacial acetic acid. These solutions are suitable for preparing standards corresponding to 1/100 gr., 1/150 gr., and 1/200 gr. of glyceryl trinitrate. In each case 0.25 c.c. of the solution of diphenylamine is added to 1 c.c. of these solutions, and after mixing while the tubes are suspended in cold water for three minutes, glacial acetic acid is added to bring the volume up to 10 c.c. The estimation must then be made within ten minutes before the blue colour begins to fade.

Assay showed that there was little variation in the strength of tablets taken from batches freshly prepared and stored in screw-capped bottles or corked containers. All tablets manufactured in bulk which were examined contained between 80 per cent. and 100 per cent. of the estimated amount of glyceryl trinitrate, so that there is no appreciable error involved in the method of manufacture. There was, however, considerable variation in the strength of tablets taken from constantly opened bottles after storage for six weeks or longer; a proportion of the tablets contained only 70 per cent. of their supposed content of glyceryl trinitrate. The tablets deteriorated

markedly when they were stored for a long period, especially if they were in opened containers. One batch after storage for eight months in an open container at room temperature contained only 30 per cent. to 70 per cent. of the estimated amount of glyceryl trinitrate in each tablet, and only one out of six examined contained more than 50 per cent. of the proper dose. The tablets also deteriorated markedly when exposed to heat.

These considerations suggest that definite regulations should be introduced regarding the sale, storage, and assay of glyceryl trinitrate tablets. They should be issued in sealed screw-capped or waxed corked bottles, as adopted by some firms at present, and should be used within two months of manufacture, especially if the container is opened frequently. The date of manufacture and batch number should be stated on the container. If a considerable number of tablets are given to patients at one time for use for more than a month they should be issued in screw-capped bottles by the dispenser in order to minimize deterioration.

All tablets used in the present investigation were obtained fresh from the manufacturers or were specially prepared in the hospital dispensary, and every batch was assayed by the method described above. The gelatine capsules of glyceryl trinitrate dissolved in oil were made by Martindale and contained 1/100 or 1/30 gr. (0.0006 or 0.002 grm.) of the drug. These and the proprietary remedies tested were not assayed as the method did not give satisfactory results because of the vehicles used.

*Absorption of glyceryl trinitrate (trinitrin).* Difference of opinion on the value of glyceryl trinitrate has led to doubt whether the drug is absorbed effectively from the stomach. Janeway (47) was the first to emphasize the importance of correct administration. He insisted that tablets of the drug should be taken on the tongue and not swallowed because absorption from the mouth was more rapid than from the stomach, though he did not give supporting evidence. He considered that swallowing the tablets accounted for many reported failures. Brunton (12) made no comment upon the relative values of the alcoholic solution and tablets, but he did advise that the latter should be slowly nibbled and not swallowed. Allbutt (1) mentioned that the alcoholic solution acted better, although the tablets were more convenient. Vaquez (91) also preferred the alcoholic solution because tablets dissolved too slowly in the mouth.

In 1923 Grossman and Sandor (31) reviewed the therapeutic action of glyceryl trinitrate and pointed out that although its prompt effect as a vasodilator was well established, there was no unanimity regarding the best method of administration or the most suitable dose. They cited the contradictory statements regarding the effectiveness of glyceryl trinitrate tablets. They compared the effects of an alcoholic solution of the drug upon the pulse and blood-pressure, when absorbed from the mouth and when given by stomach or duodenal tube. The method of administration decided the extent to which tachycardia and fall in blood-pressure occurred. These effects were produced quickly when absorption took place in the mouth;

they were much less evident and delayed when the drug was swallowed, and were almost absent when the drug was introduced directly into the stomach or duodenum. The same differences were observed with the tablets; soft tablets which dissolved readily in the mouth acted much more effectively than those which were swallowed; the latter had an uncertain effect or none at all. They did not find any essential difference in the action of an alcoholic solution and the tablets. The deciding factor in the rapidity and extent of the action of the drug was the time allowed for absorption from the buccal mucous membrane. Although previous clinical experience had already suggested the practical importance of this detail of administration, it appears to have received no further attention until this present investigation.

The rate of absorption of glyceryl trinitrate from the mouth and stomach was estimated in four healthy adults and in one patient for whom gastrostomy had been performed for carcinomatous obstruction in the oesophagus. Here, by introducing the drug directly into the stomach, it was possible to exclude absorption from the mouth and oesophagus which might occur even when the drug was swallowed quickly. During each observation the blood-pressure readings and the pulse-rate were recorded at intervals of one to two minutes and symptoms were noted as they occurred. Whenever absorption from the stomach was tested the subjects had always fasted for a period of three hours or longer. The preparations used contained 1/30 gr. (0.002 grm.) of glyceryl trinitrate. The following methods of administration were employed:—glyceryl trinitrate in tablet form with chocolate basis was well chewed and allowed to absorb from the mouth, or was swallowed quickly in powder form, or as whole tablets; glyceryl trinitrate in oil contained in a gelatine capsule was broken in the mouth; liquor glycerylis trinitratis (B.P. 1932) was dropped on the tongue. In the patient with gastrostomy, glyceryl trinitrate in powder form was also introduced directly into the stomach through the tube.

Typical results are shown in Figs. 1 and 2. Glyceryl trinitrate when chewed and absorbed from the mouth acted quickly. It produced noticeable tachycardia in  $1\frac{1}{2}$  minutes which increased up to  $2\frac{1}{2}$  minutes and then gradually subsided with a return to normal in less than 10 minutes (Fig. 1). Sensations of fullness and throbbing in the head also occurred within  $1\frac{1}{2}$  minutes and never persisted after 10 minutes. The blood-pressure was never materially affected in the four younger subjects, although a slight temporary fall in the systolic blood-pressure was sometimes noticed. A very prominent fall in both systolic and diastolic blood-pressure occurred in the elderly and weakly patient with gastrostomy (Fig. 2).

When glyceryl trinitrate was swallowed quickly in powder form only a small degree of tachycardia was noticed two to eight minutes afterwards (Fig. 1); there was seldom any change in blood-pressure and symptoms were usually absent, but if present their onset was delayed and they were of short duration. In this test it was impossible to exclude slight absorption

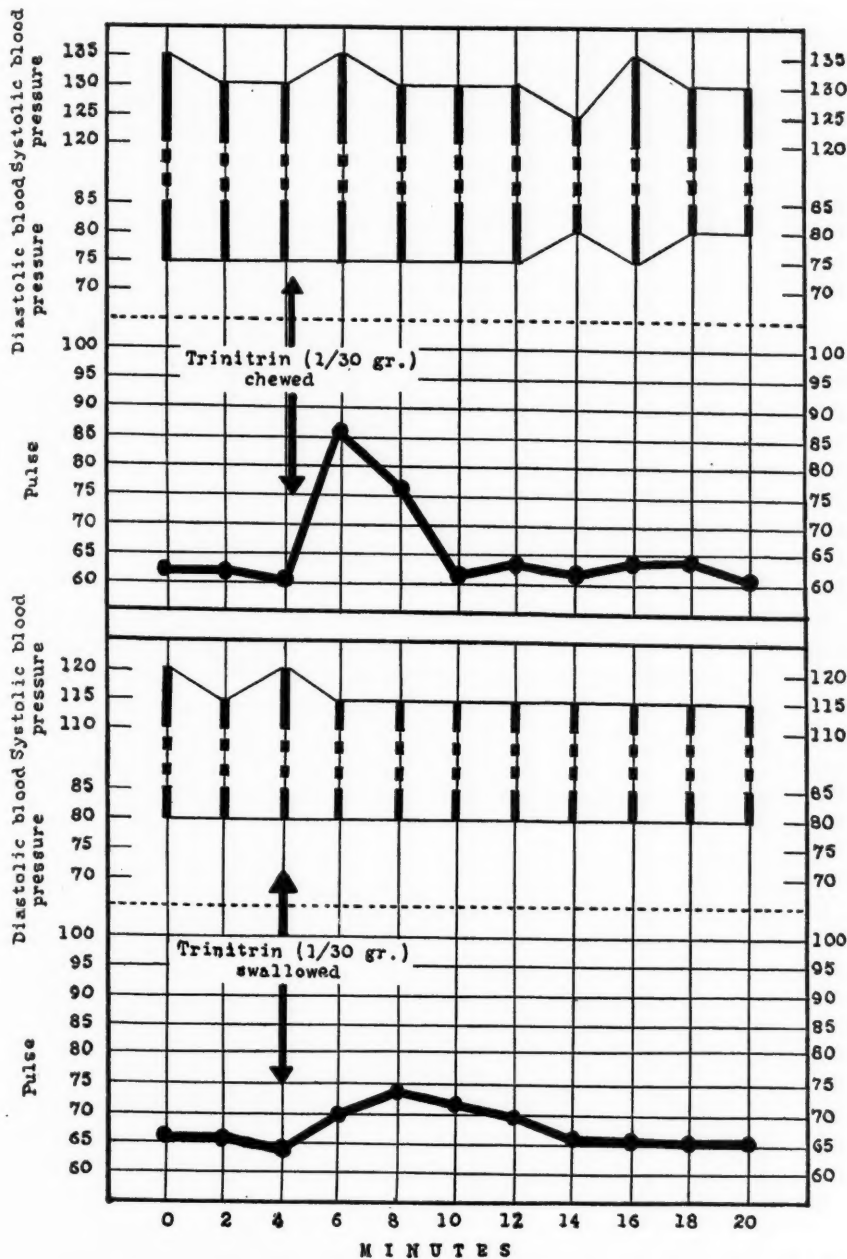


FIG. 1. Illustrating the effects of glyceryl trinitrate (trinitrin) on the pulse-rate and blood-pressure in a male, aged 23 years, when chewed and when swallowed.

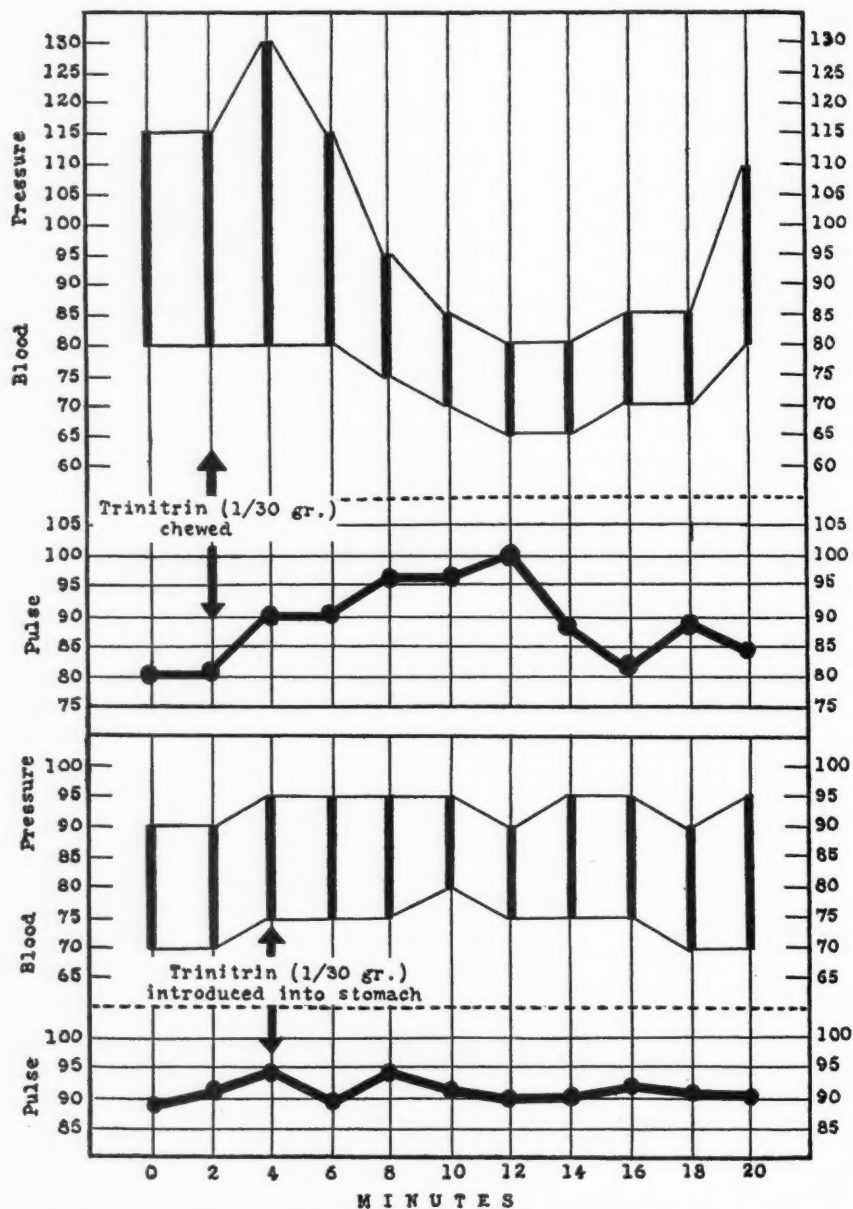


FIG. 2. Illustrating the effects of glyceryl trinitrate (trinitrin) on the pulse-rate and blood-pressure in a male, aged 71 years, in whom gastrostomy had been performed for carcinomatous obstruction of the oesophagus. The first tracing was recorded after chewing trinitrin, and the second following direct introduction of trinitrin into the stomach.

from the mouth and also to a lesser extent from the oesophagus during swallowing. Although this was done as quickly as possible and was aided by taking a little water, the powder had rested three seconds on the tongue. That this allowed some degree of absorption is shown by the observation made on the gastrostomy patient where absorption from the mouth and oesophagus was excluded (Fig. 2).

Gelatin capsules of glyceryl trinitrate in oil 1/30 gr. (0.002 grm.) produced tachycardia when chewed, but the onset was delayed and usually did not appear for three minutes. Similarly, general symptoms were delayed and lasted for a shorter period. When a fall in systolic blood-pressure occurred it was slight.

Liquor glycerylis trinitratis (3 minims (0.2 mls.) containing 1/30 gr. (0.002 grm.) of glyceryl trinitrate) produced noticeable tachycardia usually within  $1\frac{1}{2}$  to 2 minutes. There was a slight temporary fall in the systolic blood-pressure but the diastolic blood-pressure was not affected. Symptoms were slight and usually only lasted from two to five minutes. In order to exclude contributory effects from its alcoholic basis, separate tests were carried out with 10 drops of absolute alcohol, but there were never any changes in pulse-rate and blood-pressure, or any general symptoms.

The practical importance of these results is that the anginal patient must chew glyceryl trinitrate tablets thoroughly to ensure rapid therapeutic action from immediate absorption of the drug from the mouth. If the tablets are swallowed whole, or broken in the mouth and then swallowed quickly, they are of slight or no value in treatment.

*Scheme of therapeutic observations.* Most of the patients visited the Department at fortnightly or monthly intervals. All who were not co-operative were soon allowed to fall out of the series; the remaining ones were judged to be trustworthy. Even so they were closely questioned, and were often admitted to hospital for confirmatory observations. While attending the Department each patient made personal records of every attack, and these were entered on a special form at each attendance. Details were noted of the severity and duration of attacks and the nature of the exercise which had induced pain. Particular attention was directed to duration of the attacks when rest was the only treatment. Patients were persuaded to time them by their watch as the duration of pain would vary with exertion. In this way a certain standard could be formulated of the duration of attacks under no treatment other than rest. This standard was subsequently used when comparing the effects of the various remedies in the same individual. Each patient made similar observations upon attacks in which the remedies were tried. The proper method of administration was explained to each patient, and he was warned that he might experience incidental symptoms such as giddiness, flushing, palpitation, and throbbing in the head, when using nitrite and chloroform. A summary of the previous fortnight's trial was made at each visit and then the observations required of the patient during the next test period were explained. When there had been

sufficient repetition we gained the patient's considered opinion upon the respective values of the various remedies. After using the ordinary therapeutic dose this was doubled or trebled and again similar observations were made both by the patients and ourselves. Later they were asked to continue the exertion which had induced pain in order to compare the effectiveness of remedies in ordinary and excessive doses, both during exercise and when rest was taken from the onset of pain. The results are discussed in four groups indicating different degrees of clinical improvement as follows:— (a) great relief indicating a decrease of more than 50 per cent. in the duration of attacks; (b) moderate relief, indicating a decrease of less than 50 per cent. in the duration of attacks; (c) no relief; (d) worse.

The effectiveness of each drug in *preventing* the onset of an expected attack was then studied. Patients had to record the prophylactic effect of a drug when taken immediately before or at intervals of five to thirty minutes before an exercise which habitually induced pain, and to compare their freedom from pain, when walking measured distances both without and with the aid of a drug. Our own observations were made in a few particular patients during exercise over a standard itinerary of 360 yards in the hospital's grounds and a standard climb of 123 steps on a staircase. The walk provided two steep and two moderate gradients. The exertion test was controlled and timed, and frequent blood-pressure readings were made during trials of the efficacy of the various remedies both for the relief of attacks and for their prevention. The dose required to produce the desired effect was determined in this way. The results are again discussed in four groups, indicating the clinical response as shown by a decrease in the number of attacks when compared with control observations during which no drug was taken to prevent pain.

### Results

The results obtained with each drug will be discussed separately and will be prefaced by a summary of the literature. A further section will review the comparative effects of the drugs tested, both for the immediate treatment of attacks and for their prevention.

*Glyceryl trinitrate* (Nitroglycerin: trinitrin.). Glyceryl trinitrate was not introduced as a remedy for angina pectoris until 1879 when Murrell (63) recorded three patients who were greatly relieved by using the drug by mouth in a 1 per cent. alcoholic solution. The following year Robson (75) confirmed Murrell's observations, and interest soon became focused upon details of its administration, its value compared with amyl nitrite, and its occasional failure to relieve. Murrell's use of an alcoholic solution by mouth became the common method of administration for a time. Glyceryl trinitrate tablets were introduced by Martindale in 1878 and have been official since the Pharmacopoeia of 1885. A few writers (28, 43, 5) have since

mentioned hypodermic administration in severe attacks, but this is impracticable for continued use.

There is still a division of opinion whether glyceryl trinitrate or amyl nitrite is the more valuable for attacks. Powell (68) thought that glyceryl trinitrate was more reliable than amyl nitrite, and this view was shared by Duroziez (18). Huchard (43) preferred amyl nitrite because it acted almost immediately whereas glyceryl trinitrate required four to five minutes. Schott (79) stated that glyceryl trinitrate was superior to amyl nitrite in most cases and Ferreira (23) also preferred it because the effects were more lasting. Allbutt (1) thought it certainly more efficacious, though he admitted that amyl nitrite acted more quickly. Since then opinion has remained divided, though glyceryl trinitrate has gained favour (83, 39, 49, 61, 94).

The prophylactic use of glyceryl trinitrate in angina was mentioned by Murrell (63) in his original paper. He found great improvement in four patients from the use of 1 to 10 minims of a 1 per cent. alcoholic solution taken every three or four hours. The patients used additional doses to prevent threatened attacks and no ill effects were noted. Robson (75) also mentioned the prevention of attacks by glyceryl trinitrate without ill effects and Himmelsbach (40) recorded one patient who had experienced such benefit from the drug that for seven years he had taken 80 to 110 tablets (each containing 1/100 gr., 0.0006 grm.) of glyceryl trinitrate daily without detriment. At one period under observation this patient took as many as 1,000 tablets, 1/50 gr. (0.0012 grm.) each, daily for eight consecutive days. Osler (66) recommended tablets four or five times daily apart from attacks and remarked that the drug was often given in insufficient doses. Leech (52, 53) stressed the value of glyceryl trinitrate as a prophylactic measure both in his Croonian lectures and in his book. He advised that a sufficient dose should be given a few minutes before an exertion which was likely to cause an attack of pain. A suitable dose varied from 1 to 25 minims or more of the 1 per cent. alcoholic solution, and he said that he considered that danger lay not in the size or frequency of the dose but in the fear to use the drug freely. White (94) considered that glyceryl trinitrate may be specially valuable when taken four or five minutes before some necessary effort, like evacuation of the bowels, which may bring on pain.

In spite of this strong recommendation of glyceryl trinitrate to prevent pain there has not been any further investigation of the subject, and it certainly has not become routine treatment. A few writers (1, 46, 60, 83, 70, 35) have mentioned it briefly, but others (12, 82, 91, 39, 49, 77, 7, 87) have ignored it. Babcock (3) frankly condemned the use of nitrites except for relieving attacks. Clearly further information is needed about the prevention of attacks by glyceryl trinitrate, and especially whether its use is dangerous. Opinion is also divided on the frequency and severity of general symptoms which follow administration of glyceryl trinitrate. Field (24) noted that headache often occurred after taking one drop of a 1 per cent.

TABLE I. *Summarizing the Effects of Drugs Tried in the Immediate Treatment of Attacks of Angina Pectoris (Angina of Effort). Numerals in Brackets Indicate Percentages.*

Drug.	Number of patients.	Patients arranged in groups according to response to treatment.				Objectionable effects.		
		Great relief. (a)	Moderate relief. (b)	No relief. (c)	Worse. (d)	Marked.	Slight.	None.
Tablets	122	105 (86)	13 (11)	4 (3)	—	2 (1.5)	28 (23)	92 (75.5)
The 1 per cent. liquor	24	15 (62.5)	5 (20.5)	4 (17)	—	1 (4)	7 (29)	16 (67)
Oily solution	26	7 (27)	10 (38.5)	9 (34.5)	—	3 (11.5)	9 (34.5)	14 (54)
Natirose dragées (Nati- velle)	42	22 (52.5)	19 (45)	1 (2.5)	—	1 (2.5)	12 (28.5)	29 (69)
Nitrolingual capsules (Pohl)	27	5 (18)	11 (41)	11 (41)	—	—	5 (18.5)	22 (81.5)
Trinitrine caféinée (Dubois)	22	11 (50)	7 (32)	4 (18)	—	1 (4.5)	3 (13.5)	18 (82)
Amyl nitrite	63	27 (43)	23 (36.5)	10 (16)	3 (4.5)	48 (76)	12 (19)	3 (5)
Sodium nitrite	29	8 (27.5)	13 (45)	7 (24)	1 (3.5)	2 (7)	14 (48)	13 (45)
Brandy	16	3 (19)	5 (31)	7 (44)	1 (6)	—	2 (12.5)	14 (87.5)
Chloroform	16	5 (31)	6 (38)	4 (25)	1 (6)	10 (62)	3 (19)	3 (19)
Carminatives	12	3 (25)	3 (25)	6 (50)	—	2 (17)	2 (17)	8 (66)

alcoholic solution, and Brady (6) described unconsciousness with convulsions after  $2\frac{1}{2}$  drops of a 5 per cent. solution. Harley and Fuller (34), about the same time, reported far slighter effects and held that the drug could be taken with impunity in fairly large doses. Murrell (63) described in detail the symptoms produced in himself and thirty-five other subjects by doses up to 15 minims of a 1 per cent. alcoholic solution. Pulsation in the head with a sense of fullness and heat over the body and occasionally a severe headache and drowsiness were the most prominent symptoms, but only lasted about a quarter of an hour except headache, which sometimes persisted for several hours. He gave doses up to 10 minims (0.6 mils.) at intervals of three to four hours to patients with angina pectoris without any serious complaints, but larger doses than this led to headache. Brunton (11) mentioned that troublesome headache may follow glyceryl trinitrate and suggested using very small doses. The rarity of serious effects has received general recognition (75, 97, 72, 65, 74, 46, 57, 87). In 1902 Leech (53) was only able to cite one recorded instance in which a fatal result could be attributed to the medicinal use of nitrite compounds. Occasionally temporary collapse has been described due to idiosyncrasy (42, 55, 95, 69). There are also numerous records of remarkable tolerance to the drug (84, 85, 17, 40, 62, 51, 19, 38). Martindale (59) recorded an employee who ate a piece of glyceryl trinitrate mass weighing 2 oz.; he suffered from no ill effects beyond a bad headache, and returned to work on the following day. Allbutt (1) mentioned that increasing tolerance may result when the drug is given often. Myers and Austin (64) recorded a patient who failed to respond to 500 times the initial dose after six months' use of the drug. They believed that tolerance usually lasted only a short time.

In the present investigation glyceryl trinitrate ( $(1/100$  or  $1/50$  gr.) (0.0006 or 0.0012 grm.)) was prescribed in tablet form with chocolate or lactose as basis. The chocolate tablets were more commonly used, though the lactose tablets suited edentulous subjects better as they dissolved readily on the tongue and did not require to be chewed.

The effects of glyceryl trinitrate tablets in the treatment of the anginal attack was estimated in 122 patients. One hundred and five (86 per cent.) obtained great relief (*a*), 13 (11 per cent.) moderate relief (*b*), and 4 (3 per cent.) no relief (*c*) (Table I). The effects were estimated both when the patient resorted to rest at onset of the pain and when the exercise which had induced pain was continued. Some of the patients found that half a tablet ( $1/200$  gr., 0.0003 grm.) produced immediate relief, while a few found it necessary to take three tablets ( $1/30$  gr., 0.002 grm.) in order to resolve an attack quickly. Slight objectionable effects such as flushing, throbbing, and a sensation of warmth and fullness in the head, or slight headache were experienced by 28 (23 per cent.), and these symptoms were more pronounced and associated with severe headache in only two (1.5 per cent.). In 92 (75.5 per cent.) no general symptoms were recorded. Tolerance to the drug, as shown by a decrease in general symptoms or diminished

therapeutic effect of a given dose, was never met, even though almost all the patients continued to take the drug for two to three years.

TABLE II. *Summarizing the Effects of Drugs Tried in the Immediate Prevention of Attacks of Angina Pectoris. Numerals in Brackets Indicate Percentages.*

	Drugs.	Number of patients.	Patients arranged in groups according to response to treatment.		
			Great benefit. (a)	Moderate benefit. (b)	No benefit. (c)
Glyceryl trinitrate.	Tablets	72	61 (84.5)	9 (12.5)	2 (3)
	The 1 per cent. liquor	18	8 (44.5)	3 (16.5)	7 (39)
	Oily solution	19	4 (21)	3 (16)	12 (63)
	Natirose dragees (Nati- velle)	21	9 (43)	7 (33)	5 (24)
	Nitrolingual capsules (Pohl)	22	3 (14)	6 (27)	13 (59)
	Trinitrine caféinée (Dubois)	17	7 (41)	6 (35.5)	4 (23.5)
	Sodium nitrite	30	11 (36.5)	6 (20)	13 (43.5)
	Amyl nitrite	63	—	4 (6.5)	59 (93.5)
	Brandy	11	1 (9)	—	10 (91)
	Chloroform	14	1 (7)	—	13 (93)
	Carminatives	10	—	1 (10)	9 (90)

The value of glyceryl trinitrate tablets in *preventing* the onset of expected attacks was estimated in 72 patients. They were asked to take the drug at definite intervals before the expected onset of pain. In practice this usually meant that a patient chewed a tablet of trinitrin before walking out of his home or before commencing some other form of exercise which regularly induced pain. Of the 72 patients who used the drug in this way 61 (84.5 per cent.) benefited greatly (a), 9 (12.5 per cent.) moderately (b), and only 2 (3 per cent.) not at all (c). (Table II and Fig. 3. Diary in Appendix). The number of tablets of 1/100 gr. (0.0006 grm.) taken to secure the greatest measure of relief varied up to twenty daily according to the individual, the liability to pain, and the exertion undertaken. When patients learned that glyceryl trinitrate used in this way allowed more physical exercise the number of tablets which they took was often correspondingly increased.

In order to be certain that the use of glyceryl trinitrate for the prevention of attacks is safe, it is necessary to show that the drug may be given

in this way for months or even years without ill effects. We were able to observe 47 of our patients for a sufficiently long period to be convinced that the risks of sudden death or of toxic effects are negligible. Nineteen of these were under observation for periods up to two or three years, and during this time they took up to twenty-six tablets daily, each containing 1/100 gr. (0.0006 grm.). Not one of the 47 suffered from any ill effects attributable to the drug.

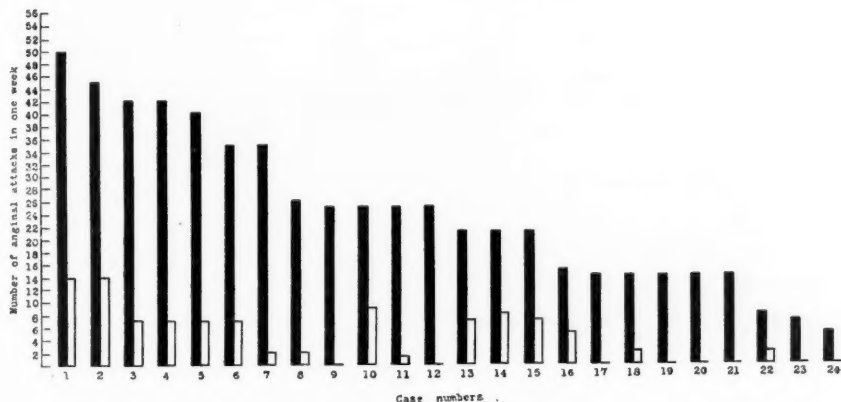


FIG. 3. Illustrating the effect of the prophylactic use of glyceryl trinitrate (trinitrin) tablets on the incidence of anginal attacks in 24 patients in our series. The black columns represent the number of attacks in each patient when tablets were not used to prevent them. The unshaded columns indicate the number of attacks when each patient took glyceryl trinitrate tablets (gr. 1/100) at his own discretion to prevent the onset of expected pain. The attacks are markedly diminished in all, while 8 remained free from attacks following the prophylactic use of the tablets. The observation was repeated on several occasions and care was taken to exclude the occurrence of natural variation in the incidence of attacks in these results.

As these results show that a very great measure of relief is afforded by glyceryl trinitrate when used prophylactically at the discretion of the individual, we also wished to know what relief might follow its regular administration at short intervals of an hour or less throughout the day. This was investigated in 17 of the most co-operative patients. Ten obtained great benefit from hourly administration, and six of these, who formerly had an average of six attacks daily, remained completely free from pain during the trial. Four obtained moderate benefit. The remaining two patients did not benefit as estimated by a reduction in the number of attacks. Five patients complained of fairly severe and three of slight general symptoms. Four patients taking glyceryl trinitrate 1/100 gr. (0.0006 grm.) half-hourly during a twelve-hour day for seven consecutive days did not complain of any unpleasant effects, while one patient complained only of a little giddiness, although taking 1/50 gr. (0.0012 grm.) half-hourly during a twelve-hour day for five consecutive days, when he had ingested 2.8 gr. (0.168 grm.) of glyceryl trinitrate. All 17 patients obtained at least an equal measure

of improvement from using the drug prophylactically at their own discretion and 5 preferred to do this. Fig. 4 illustrates the results in one patient.

These observations made by patients on the value of glyceryl trinitrate in relieving and preventing the anginal attack were frequently reviewed by us over the *standard walk and climb*.

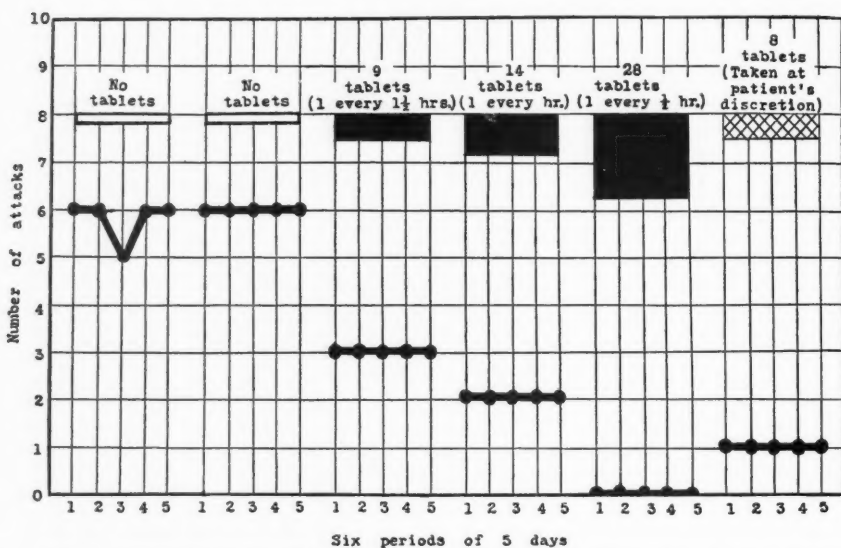


FIG. 4. Illustrating the effect of glyceryl trinitrate (trinitrin) tablets on the incidence of anginal attacks in a male, aged 59 years. The unshaded columns represent two control periods of 5 days when glyceryl trinitrate was not used prophylactically. The black columns represent three periods when patient took 9, 14, and 28 tablets (gr. 1/50) daily at intervals of 1 1/2, 1, and 1/2 hour. The shaded column indicates a period when the patient only took 8 tablets daily, using them at his own discretion for the prevention of expected attacks. The observation was repeated so that natural variation in the incidence of attacks can be discounted.

As a better conception of the benefit which patients with angina derive from the use of glyceryl trinitrate for the prevention of pain can more often be obtained from the records of individual patients than from statistical analysis, a selected number of these records have been given in the Appendix. We have never found that the prevention of attacks has proved to be dangerous, and it has allowed patients to take exercise which would have been impossible otherwise.

*Liquor glycerylis trinitratis.* The 1 per cent. alcoholic liquor trinitrini B. P. 1914) now liquor glycerylis trinitratis (B. P. 1932) keeps well and does not require assay because it can be prepared accurately in bulk. It was prescribed undiluted from a small drop-bottle. The dose was 10 minims (0.6 mils.) (1/12 gr. or 0.005 grm.) dropped on to a small piece of sugar which was then chewed quickly. It was tried for the relief of attacks in 24

patients. Fifteen (62.5 per cent.) obtained great relief (a), 5 (20.5 per cent.) moderate relief (b), and 4 (17 per cent.) no relief (c) (Table I).

The effects of the liquor in preventing anginal attacks were observed in 18 patients. In 8 (44.5 per cent.) there was great benefit (a), in 3 (16.5 per cent.) moderate (b), and in 7 (39 per cent.) no benefit (c) (Table II).

Slight general symptoms occurred in 7 (29 per cent.) and these were marked in only one (4 per cent.) patient. The remaining 16 (67 per cent.) experienced no unpleasant symptoms.

*Glyceryl trinitrate in oil.* The effects of an oily solution of glyceryl trinitrate ((1/100 gr.) (0.0006 grm.)) in gelatine capsules were tested in 26 patients. The capsules were broken in the mouth, and chewing the gelatine lining tended to neutralize the unpleasant oily taste. When used for the relief of attacks only, 7 (27 per cent.) patients obtained great relief (a), 10 (38.5 per cent.) obtained moderate relief (b), and 9 (34.5 per cent.) obtained no relief (c) (Table I).

Its prophylactic effects were estimated in 19 patients and only 4 (21 per cent.) of these gained great benefit (a), and 3 (16 per cent.) moderate benefit (b) (Table II).

Twelve (46 per cent.) of the 26 patients experienced general symptoms which were slight in 9 and severe in 3. In the remaining 14 (54 per cent.) there were no unpleasant effects.

*Proprietary preparations.* 1. *Natirose dragees (Nativelle).*<sup>1</sup> Natirose dragees were tested for the relief of attacks in 42 patients. One or two dragees were chewed during attacks. Twenty-two (52.5 per cent.) patients obtained great relief (a), 19 (45 per cent.) moderate relief (b), and one (2.5 per cent.) no relief (c) (Table I).

The prophylactic effect of dragees was estimated in 21 patients. Nine (43 per cent.) obtained great benefit (a), 7 (33 per cent.) moderate (b), and 5 (24 per cent.) no benefit (c) (Table II).

General symptoms occurred in 13 (31 per cent.) of the 42 patients, but they were severe in only one. Twenty-nine (69 per cent.) did not complain of any unpleasant effects.

2. *Nitrolingual capsules (Pohl).*<sup>2</sup> Nitrolingual capsules were tested for the relief of attacks in 27 patients. Only 5 (18 per cent.) obtained great relief (a), 11 (41 per cent.) patients obtained moderate relief (b), and 11 (41 per cent.) no relief (c) (Table I).

In 22 patients they were tried for the prevention of attacks. Only 3 (14 per cent.) obtained great benefit (a), 6 (27 per cent.) moderate, and 13 (59 per cent.) no benefit (c) (Table II).

Five (18.5 per cent.) patients out of 27 complained of slight symptoms.

<sup>1</sup> Each dragee contains 1 per cent. solution of glyceryl trinitrate (0.0045 grm.), 0.0003 grm., of dionin, 0.00001 grm., of atropine sulphate, and essence of peppermint.

<sup>2</sup> Each capsule contains 0.0008 grm. of glyceryl trinitrate flavoured with essence of peppermint.

3. *Trinitrine caféinée pills (Dubois).*<sup>3</sup> Trinitrine caféinée pills (Dubois) were tried for the relief of attacks in 22 patients. Eleven (50 per cent.) obtained great relief (a), 7 (32 per cent.) moderate relief (b), and 4 (18 per cent.) no relief (c) (Table I).

Their prophylactic effects were recorded in 17 patients. Seven (41 per cent.) of these obtained great benefit (a), 6 (35.5 per cent.) moderate (b), and 4 (23.5 per cent.) no benefit (c) (Table II). General symptoms were noticed by 4 (18 per cent.) patients only, and they were slight except in one.

If these results with proprietary preparations of glyceryl trinitrate are considered collectively, 40 per cent. of the patients obtained great relief (a) from their use in attacks, 39.5 per cent. moderate relief (b), and 20.5 per cent. no relief (c). When used for the prevention of attacks 32.5 per cent. obtained great benefit (a), 32 per cent. moderate benefit (b), and 35.5 per cent. none (c). General symptoms occurred in 22.5 per cent. Thus, when compared with glyceryl trinitrate tablets, these proprietary preparations are less satisfactory both for the relief and the immediate prevention of attacks.

*Amyl nitrite.* Richardson (71), who gave one of the first accounts of the physiological action of amyl nitrite, regarded the drug as a curiosity, and did not recommend its trial in medicine at that time. Shortly afterwards Lauder Brunton (8, 9) gave a full account of its action as a vasodilator, and tried it for anginal attacks. In one patient, attacks which normally lasted for an hour or more were relieved in less than a minute by the inhalation of three to five minims (0.2 to 0.3 mls.) of the drug. Supporting observations soon followed (89, 10, 2, 81, 33, 48, 96, 58, 20) and till recently amyl nitrite held the first place among the remedies for attacks.

Subsequent writers have added little to our knowledge of the drug, though attention has been drawn to the fact that it is sometimes ineffective, and at times even dangerous. Ticehurst (90) was the first to record failure to obtain relief from anginal pain by amyl nitrite, but the account suggests that the case was one of coronary thrombosis. Both Jones (48) and Huchard (42) mentioned that the dose had to be increased sometimes to twenty drops or even more because tolerance developed rapidly. Yeo (97) and Gibson (29) maintained that amyl nitrite did not always give relief, and Greene (30) thought that nitrite was useless except for the briefest attacks. Allbutt (1) noted that amyl nitrite was not effective in some patients, and that it acted unpleasantly. He believed that it was falling out of favour. Osler (65) in his lectures stated that it was singularly uncertain, sometimes quite inert, and might produce its physiological effects without relieving pain. Leech (52, 53) regarded these failures as due either to a wrong diagnosis, shortness of the nitrite action, personal insusceptibility to the drug, or to its trial in an advanced case 'where attacks of pain continue long'. He was the first to recognize that it was ineffective in prolonged attacks, which are known to be due to coronary thrombosis. Apart from these, occasional cases of angina

<sup>3</sup> Each pill contains 1 per cent. solution (0.03 grm.) of glyceryl trinitrate and 0.02 grm. of caffeine.

pectoris of effort fail to get relief or may even experience greater pain. Ingals and Meeker (46) recorded a patient who obtained no relief from amyl nitrite, but rapid relief from glyceryl trinitrate. Romberg (76, 77) has stated that he has hardly ever seen relief from amyl nitrite at the height of the attack. It has not been known how often it fails when coronary thrombosis can be excluded.

The general symptoms due to amyl nitrite were first accurately described by Guthrie (32) and Jones (48), and they have been particularly stressed by writers who have preferred other nitrites. Janeway (47) referred to its objectionable odour, and as the drug was not more effective than glyceryl trinitrate he preferred the latter. Marvin (61) recently noted that most patients objected to amyl nitrite because of the discomfort which followed and because its inhalation attracted attention. There has not been any comparative investigation into the severity of these general symptoms in a series of patients, nor a record of the extent to which these have influenced patients in choosing a remedy, though really harmful effects from amyl nitrite seem to have been rare. A few instances of temporary collapse after big doses have been recorded (78, 27, 80).

Although its action is so short, amyl nitrite has been said to have a prophylactic action in preventing or lessening the incidence of attacks (81, 58, 20, 43). The evidence is unconvincing.

In our series amyl nitrite was always taken by inhalation from glass capsules containing 5 minims (0.3 mils.). Patients were instructed to break the capsule in a handkerchief and hold it close to the nose, then to inspire through the nose and expire through the mouth.

Amyl nitrite readily decomposes and becomes inert when exposed to air or light, so that glass capsules of the drug are the only satisfactory means of keeping the drug ready for use. They are sealed out of contact with air and contain an accurate dose of the drug which keeps indefinitely if not exposed to light. Martindale (59) refers to a batch which was fully active after being stored for seventeen years. It is not known how far capsules keep well in the tropics.

Many capsules on the market have the serious disadvantage that the glass container is too thick and cannot be broken readily, so that immediate inhalation of the drug during an anginal attack is more than prejudiced. We have tested nine commercial makes of capsules for the ease with which they can be broken. Those supplied by six reputable firms could often not be broken by strong pressure between the finger and thumb. Three others consistently satisfied our requirements, and of these we used Martindale's for the investigation.

Amyl nitrite was repeatedly tried by 63 patients for the relief of their attacks. Twenty-seven (43 per cent.) obtained great relief (*a*), 23 (36.5 per cent.) moderate relief (*b*), 10 (16 per cent.) no relief (*c*), and 3 (4.5 per cent.) experienced increased pain (*d*) (Table I).

Only 4 (6.5 per cent.) patients seemed to gain any prophylaxis from using amyl nitrite. Even in these it was limited to brief periods (Table II).

Sixty of the 63 patients complained of incidental symptoms. In 48 (76 per cent.) vertigo, palpitation, and headache were so objectionable that it was impossible to persuade them to continue its use. Without exception they much preferred glyceryl trinitrate.

*Sodium nitrite.* There are few references to the use of sodium nitrite during individual anginal attacks or for the immediate prevention of pain. Hay (36), in his original paper, recorded one patient in whom relief was less rapid but more complete than with amyl nitrite. Trying it for the immediate prevention of attacks, his patient took 1 gr. (0.06 grm.) or more before undertaking any exertion which was known to induce pain. Thus, a single dose taken before rising in the morning enabled him to get up, dress, breakfast, and walk to his work without pain. Sodium nitrite had a preventive action superior to amyl nitrite and appeared to be rather better than glyceryl trinitrate in that relief lasted longer. Hay noted the absence of any disagreeable general symptoms from the drug, except that eructations occurred after large doses. His patient did not develop tolerance. In the same year Collier (15) reported considerable prophylaxis in one patient from using 3 gr. (0.2 grm.) about ten minutes before doing anything likely to induce pain. Lublinski (56) agreed with Hay that sodium nitrite took five to eight minutes to produce a noticeable therapeutic effect, though this might last for as long as three to four hours. Gélinau (28) mentioned that he had seen good results from its use in attacks, while Huchard (43) hesitated to use it because of the risk of methaemoglobinaemia, but now we know that this does not occur with therapeutic doses. Neither Leech (52), nor Osler (65) in his lectures, nor Brunton (12) in his book, mentioned sodium nitrite for the treatment of individual attacks. Leech advised the drug for prophylaxis when glyceryl trinitrate was not well borne on account of headache, but he admitted that it did not usually agree so well. Ringer and Sainsbury (73), and Barié (5), thought that it was uncertain in relieving attacks. Janeway (47) felt that all nitrites, other than amyl nitrite and glyceryl trinitrate, acted too slowly to be effective for attacks. Vaquez (91) stated that the drug had no effect in attacks, except when given hypodermically. This, however, can never be a method of choice in treatment. Cotton (16), in a general review, stated that a grain of sodium nitrite slowly dissolved in the mouth a quarter of an hour before beginning exertion may prevent pain. White (94) considered that sodium nitrite was far inferior to glyceryl trinitrate and amyl nitrite for the treatment of attacks, but that it can be used for their prevention. Romberg (77) held it to be useless in attacks whether given by mouth or by hypodermic injection, and did not comment upon prophylaxis. Brooks (7), however, claimed that the best effects are obtained by using sodium nitrite more or less constantly, but he gave no details or supporting evidence.

It is clear that opinion is general that sodium nitrite acts too slowly for it to relieve individual attacks; but there are no data available to compare its effectiveness with other vasodilators either for the relief or prevention of pain.

Sodium nitrite was prescribed as a mixture, or in tablet form, in doses of 3 to 5 gr. (0.2 to 0.3 grm.). Although at one time sodium nitrite was so largely contaminated by nitrate that it only contained about 25 per cent. of nitrite, its purity is not disputed nowadays, and it keeps so well if stored correctly that assay is not required. It was tried for the treatment of attacks in 29 patients. Eight (27.5 per cent.) obtained great relief (a), 13 (45 per cent.) moderate relief (b), 7 (24 per cent.) no relief (c) while in one patient (3.5 per cent.) it appeared to accentuate and prolong the attack (d) (Table I).

Its prophylactic effect was tested in 30 patients. Eleven (36.5 per cent.) obtained great benefit (a), 6 (20 per cent.) moderate benefit (b), and 13 (43.5 per cent.) no improvement (c) (Table II).

General symptoms, especially eructations, vertigo, and throbbing in the head were noticed by 16 (55 per cent.) patients, but they were marked in only 2 (7 per cent.).

*Brandy.* In his original account of angina pectoris, Heberden (37) referred to the value of alcoholic draughts for the prevention of nocturnal pain, but he remarked that they were not so effective as an opiate. Parry (67) also advised cordials for the relief of pain, though he mentioned one patient to whom four or five ounces of brandy brought no relief. From that time until the introduction of nitrite, alcohol and opiate constituted the most effective means of relieving angina, and in 1877 Gairdner (27) wrote that 'opiates and stimulants were still the only treatment which can be said to have received general assent'. Osler (65) and Brunton (12) both remarked that hot whisky, brandy, and spirituous carminatives (such as Hoffman's anodyne) may bring relief in attacks. Allbutt (1) spoke of the reputation of a glass of hot grog at bedtime. Ingals and Meeker (46) stated that three ounces of whisky would sometimes relieve. Martinet (60) prescribed a cocktail before indulgence in a big meal, as at a public dinner. Mackenzie (57) believed that hot drinks and alcohol sometimes gave great benefit. White (94) in his recent book writes: 'The most effective drug after the nitrites is alcohol . . . when the nitrites are not available an ounce or two of whisky, brandy, or rum will give quite rapid relief from angina pectoris, usually in the course of a few minutes.' He considers that this is an important fact to bear in mind, and that the drug may also be used cautiously as a prophylactic.

In the present series the effects of drinking one ounce (30 mls.) of neat brandy during attacks were investigated in 16 patients. Three (19 per cent.) obtained great relief (a), 5 (31 per cent.) moderate relief (b), 7 (44 per cent.) no relief (c), while in one (6 per cent.) patient the pain was made worse (d) (Table I).

One (9 per cent.) patient appeared to have benefited from the prophylactic use of brandy, but in 10 (91 per cent.) other patients there was no benefit (Table II).

Only 2 (12.5 per cent.) complained of local symptoms, which were slight.

*Chloroform.* The volatile anaesthetics, chloroform and ether, were used

for the relief of anginal pain shortly after their introduction, and were recommended by Carrière (14). Chloroform was advocated by Flint (25), Fredreich (26), Balfour (4), and Vergely (92). Huchard (45) thought that, although it produced some relief, discomfort was usual. He did not think that chloroform should be abandoned altogether, but that it should be used only when amyl nitrite and morphine failed to relieve. Gélinau (28) stressed as a disadvantage that it required skilled administration. Osler (65) thought that chloroform was more effective than ether, and advised its inhalation from a handkerchief, stating that he had never seen dangerous effects, even in persons with a 'weak heart action'. Fagge (22) stated that when pain was very severe free inhalation of chloroform was the only means of relief. Gibson (29) also held that many attacks were only amenable to chloroform or ether, but it is not clear whether he was reporting cases of coronary thrombosis. Robinson (74) regarded chloroform as dangerous at times, but advised it occasionally as the only means of relief. Brunton (12), too, recommended chloroform as an alternative to morphine in prolonged attacks, but Allbutt (1) objected to it on the theoretical ground that cardiac inhibition might result. Mackenzie (57) mentioned recurrence of pain when consciousness returned as one of its disadvantages.

In this study, inhalation of chloroform from a broken capsule containing 20 minims (1.2 mils.) was tried repeatedly for the treatment of attacks in 16 patients. Five (31 per cent.) obtained great relief (*a*), 6 (38 per cent.) moderate relief (*b*), 4 (25 per cent.) no relief (*c*), while one (6 per cent.) patient had increased pain (*d*) (Table I).

Only one (7 per cent.) patient out of the 14 experienced any benefit from its prophylactic use (Table II).

General symptoms, such as vertigo and faintness with partial loss of consciousness, occurred in 13 (81 per cent.) patients, and were severe in 10 (62 per cent.).

*Carminatives.* The use of carminatives in angina has been based upon the belief that not infrequently pain is accompanied by unrelieved flatulence. Heberden (37) noted that nocturnal angina was eased by wines and cordials which are carminatives as well as vasodilators. Parry (67), Latham (50), Stokes (86), Walshe (93), and Gairdner (27), all insisted upon the importance of flatulence as a precipitating cause of attacks and recommended wines, brandy, aromatic spirits of ammonia, or Hoffman's anodyne. Powell (68), Osler (65), Brunton (12), and Allbutt (1), all thought that carminatives were of special value. More recently Hay (35), and Brooks (7), mentioned their use in attacks, and Reid (70) advised them for prevention of pain in patients subject to flatulence. As carminative drugs are usually given in alcoholic solution, part of their action may be due to the alcohol.

In our series the effects of a carminative mixture, containing 1 drachm (4 mils.) each of the compound spirit of ether (B.P. 1914), and spirit of peppermint (B.P. 1914), taken neat, were observed in the treatment of anginal attacks in 12 patients. Three (25 per cent.) obtained great relief (*a*), 3 (25

per cent.) moderate relief (b), and 6 (50 per cent.) no relief (c) (Table I). Slight prophylactic effect was only recorded once (Table II). Local symptoms, such as a burning sensation in the mouth and throat, occurred in 4 (34 per cent.).

*The treatment and prevention of nocturnal attacks.* Heberden (37) in 1768 realized the need for treating nocturnal attacks of angina pectoris. He found that opium taken at bed-time would prevent them.

We have had experience in the treatment of 21 patients who were the subjects of nocturnal angina. In 17 of these the symptom was occasional, but in 4 it was persistent for upwards of eighteen months, and it was in these patients that we were able to observe specially the effects of certain drugs. In the majority the attacks were associated with distressing dreams. Apart from instructing each patient to take a light and early supper, and to take one or two tablets (1/100 to 1/50 gr. or 0.0006 to 0.0012 grm.) of glyceryl trinitrate at bed-time and again when awakened by the anginal attack, we investigated the effects of the following hypnotics in preventing or reducing the incidence of attacks: Morphine ( $\frac{1}{2}$  gr. or 0.03 grm.), as a tablet or cachet; pulvis ipecacuanha et opii (B.P. 1932) (20 gr. or 1 grm.); syrupus chloral (B.P. 1914) (2 drachms or 8 mils.); veronal (8 gr. or 0.5 grm.); sodium luminal (2 gr. or 0.12 grm.); a powder containing 10 gr. (0.6 grm.) each of aspirin and pyramidon with 1/6 gr. (0.01 grm.) of heroin. Each hypnotic diminished the incidence of nocturnal angina either partially or completely in individual patients, but in the four with persistent nocturnal attacks the greatest benefit was gained from the use of sodium luminal, chloral, or morphine, arranged in order of effectiveness. The investigation has led us to recommend that in any patient, the subject of nocturnal angina, the evening meal should be a light and early one, that one or two tablets of glyceryl trinitrate should be taken at bed-time and whenever awakened by an attack, and that sodium luminal, chloral, or morphine should also be taken immediately before, or an hour before, going to bed according to the time of night the patient is most susceptible to attacks.

#### *Discussion*

There is general agreement that vasodilators, and especially nitrites, are the best means of relieving individual anginal attacks. The literature shows that choice of various methods of administration is not based upon exact knowledge of their comparative values. Valuable data were collected by several observers some fifty years ago, but usually they related only to a particular drug tried in a few patients, and some of these were the subjects of coronary thrombosis.

In deciding the comparative value of vasodilators, not only has the extent to which they relieve individual attacks to be considered but also their power to prevent pain, and their freedom from disagreeable effects. In addition, the keeping properties, the readiness for use, and the price of a drug have all to be considered.

We found that glyceryl trinitrate in tablet form was by far the best remedy on all counts, provided that it was absorbed from the mouth. Patients must be instructed to chew the tablets thoroughly, or allow those with a lactose basis to dissolve in the mouth, and not merely to swallow them. For we have shown that the drug is almost inert when swallowed and when absorption has to occur from the stomach. The tablets rarely fail to relieve attacks effectively when they are used correctly; 86 per cent. (105 in 122) of the patients in our series obtained rapid and complete relief, and a further 11 per cent. (13 in 122) were relieved to a lesser degree. The necessary dose varied within comparatively narrow limits and rarely exceeded 1/50 gr. (0.0012 grm.). The tablets seldom produced severe unpleasant symptoms, which troubled only 1.5 per cent. (2 in 122) of the patients. They are convenient to carry, so that they are always available and are easy to take in attacks. They are also the cheapest of all remedies. Tablets with a lactose basis dissolve readily on the tongue and, as chewing is not necessary, they are invaluable for edentulous patients or for those where even the exertion of chewing a chocolate tablet is difficult during a severe attack. They also keep as well, do not deliquesce, are easier to assay, and retain their potency at least as well as those with a chocolate basis. As either kind of tablet deteriorates after a time some control of the condition of sale and storage is desirable.

Relieving attacks by glyceryl trinitrate is perhaps of less importance than its use for their prevention. In our series of patients the drug in tablet form almost always prevented pain when taken immediately before exertion. Eighty-five per cent. (61 in 72) of patients who used the tablets in this way obtained great benefit, and a further 12.5 per cent. (9 in 72) moderate benefit. This is a degree of improvement superior to any which occurred spontaneously or was derived from remedies used in the investigation of continuous treatment (21). A number of personal experiences given by patients which illustrate this preventive scheme of treatment are recorded in the Appendix.

A fundamental question is whether the artificial prevention of expected anginal pain is dangerous or not. In our series many patients used glyceryl trinitrate for the prevention of pain continuously for months, and often undertook physical exertion which previously had been impossible. Yet there was no instance of any harmful effect, and no death occurred which could be attributed to the drug. We conclude therefore that physical exertion may be permitted to most anginal patients instead of the rest and inactivity which has been thought to be so imperative. With the use of glyceryl trinitrate tablets for the relief and prevention of attacks 52 out of 123 patients were able to continue with their work in relative comfort. If patients are able to take physical exercise or to follow their usual occupation in comfort through the preventive use of vasodilators, then we believe that they should be permitted and in proper cases encouraged to do so.

Whether the incidence of attacks may be controlled better by administer-

ing glyceryl trinitrate at short fixed intervals, such as every hour or so, than by allowing patients to take the drug as need arises, must be decided for each individual case. When attacks cannot be predicted with certainty frequent regular administration sometimes has advantages, but general symptoms from the drug may then occur. Most of the patients who took glyceryl trinitrate every hour during the day were free from attacks, though previously there had been upwards of six a day. In some, however, hourly administration did not lead to improvement, and yet benefit resulted when the patient used his discretion in taking the drug. Most patients can predict attacks and they then derive a greater benefit from a discriminate rather than a regular administration (Fig. 4). Moreover, disagreeable general symptoms are exceptional, and none of our patients gave up this method of prevention because of them.

Nitrite administered in other ways did not give the same good results as glyceryl trinitrate tablets. The latter drug given in other forms was the next best remedy, but these cannot be recommended for general use. The alcoholic liquor glycerylis trinitratis (B. P. 1932) relieved attacks quickly in rather more than half the cases only, and it compared unfavourably with the tablets because it cannot be administered so quickly. It is also inconvenient to carry. These disadvantages preclude its regular use in treatment. Glyceryl trinitrate in oily solution failed to give any degree of relief in one-half the cases. None of the proprietary preparations of glyceryl trinitrate, namely, natirose dragees (Nativelle), nitrolingual (Pohl), and trinitrine caféinée pills (Dubois), gave results as good as the tablets, and as they are much more costly they have no claim to preference.

Amyl nitrite proved much less effective than glyceryl trinitrate tablets in relieving attacks and was valueless for their prevention. Commonly it caused unpleasant general symptoms (marked in 76 per cent. (48 in 63)) and none of 56 patients could be persuaded to continue using it after a just trial. This high figure may in part be due to the class of patient included in the series. But amyl nitrite cannot claim more than a minor place in routine treatment, and should be used only by those exceptional patients who do not get rapid relief from glyceryl trinitrate.

Sodium nitrite, although it relieved and prevented attacks in about half the patients, was much inferior to glyceryl trinitrate tablets. Objectionable symptoms were also more common, and it was unpleasant to take.

Chloroform also relieved only about half the patients and was valueless for the prevention of pain. Objectionable symptoms preclude its general use, even in the convenient form of capsules. Administration on a mask is rarely practicable.

Brandy and carminatives also gave relief in isolated cases and they are useful when other remedies are not available, but this should never be allowed to occur after a patient has come under medical supervision. Neither brandy nor carminatives prevented attacks.

Although we cannot deny that in particular patients each drug tested has

occasionally proved of value in treatment, we are abundantly satisfied that glyceryl trinitrate in tablet form when used correctly is the most efficient means of relieving and preventing anginal attacks.

### *Summary*

A series of 122 patients with angina pectoris (angina of effort) was observed over a period of three years with special reference to the comparative value of vasodilator drugs for the immediate treatment and prevention of attacks. Syphilis was present in 25 patients. Coronary thrombosis was only considered as a complication.

Each patient attended fortnightly. As a preliminary control of the therapeutic observations particular attention was paid to the duration of pain when rest was the only treatment. When an efficient standard for comparison had been obtained the following drugs were tried: glyceryl trinitrate as tablets 1/100 to 1/25 gr. (0.0006 to 0.0024 grm.), liquor trinitrini (B. P. 1914, now liquor glycerylis trinitratis, B. P. 1932) 10 minims (0.6 mils.) (1/12 gr., 0.005 grm.), and capsules of a solution in oil, 1/100 to 1/30 gr. (0.0006 to 0.003 grm.), and also as the proprietary preparations—natirose dragees (Nativelle), nitrolingual capsules (Pohl), and trinitrine caféinée pills (Dubois); amyl nitrite, 5 minims or 0.3 mils., by inhalation; sodium nitrite, 3 to 5 gr. (0.2 to 0.3 grm.); brandy, 1 oz.: chloroform, 20 minims or 1.2 mils., by inhalation; carminatives, and hypnotics. The patients' records were checked by personal observations during exercise over a measured itinerary.

The comparative results are summarized in Tables I and II, and they show that glyceryl trinitrate in tablet form when absorbed from the mouth is by far the most effective agent for relieving attacks and for their immediate prevention. Eighty-six per cent. (105 in 122) patients obtained great relief and a further 11 per cent. (13 in 122) moderate relief. Other preparations of glyceryl trinitrate and other remedies tried did not give such good results. Glyceryl trinitrate tablets should deservedly hold the first place in routine treatment. This is the more advisable because they rarely cause objectionable symptoms, they are easy to store and carry, so that they are always available for immediate use, and they are cheap. The only practical disadvantage is that they deteriorate in strength, especially when exposed to air and heat, so that they should be used preferably within two months of manufacture. Amyl nitrite proved to be disappointing for the relief of attacks, and it can only be recommended for those rare cases where glyceryl trinitrate fails to relieve. It has the further disadvantage of being useless for the prevention of attacks.

The use of glyceryl trinitrate tablets immediately before expected anginal attacks is a safe means of preventing pain and should be used far more widely in routine treatment than it is at present. In our series 84.5 per cent. (61 in 72) patients obtained great benefit, and a further 12.5 per cent.

(9 in 72) moderate benefit by using the drug in this way. This is a greater measure of improvement than was found from any of the remedies tried in our investigation of continuous treatment. Most patients preferred to take the drug at their own discretion, and this method of administration proved more effective than when it was taken at short fixed intervals, except for those patients who could not predict attacks with certainty. No harmful effects were met from such treatment, though patients used the drug freely for upwards of two to three years, and often this enabled them to take more physical exertion and lead a fuller life than had previously been possible.

We wish to acknowledge great indebtedness to our chief, Dr. John Parkinson, whose help and criticism alone made this therapeutic research possible. To other members of the Honorary Medical Staff who allowed us to observe the treatment of their patients, we owe our best thanks. It is also a pleasure to acknowledge invaluable help from Mr. C. H. Sykes, Pharmacist to the Hospital.

This investigation was made while one of us (W. E.) worked under the Paterson Bequest to the Cardiac Department, and the other (C. H.) as Medical First Assistant to the Hospital and Gillson Scholar to the Society of Apothecaries.

#### APPENDIX

A selection of personal records given by 37 patients who found great benefit from using glyceryl trinitrate tablets 1/100 gr. (0.0006 grm.) to prevent the onset of anginal attacks.

*Case 1.* M., aged 58. One tablet prevents pain during towelling: always takes one to prevent pain during a bath and another before dressing. 'If I could remember to take a tablet before commencing to walk I should have far fewer attacks.'

*Case 2.* M., aged 53. Always has pain when starting out in the morning, but now he takes a tablet before going out and he is able to walk to catch his train each morning without pain. Previously he found that when he rested to obtain relief from an attack another would commence as soon as he started to walk; after taking a tablet to relieve pain he finds that he can walk for miles without getting another attack.

*Case 3.* M., aged 35. A tablet enables him to scrub floors and clean brasses, exercises which previously induced pain. Tablets also enable him to tackle some carpentry and to start and finish the job without pain. To keep absolutely free from pain when sawing timber he requires a tablet every five minutes or so.

*Case 5.* M., aged 60. Previously pain each morning after walking a few yards, but a tablet before he leaves the house takes him as far as the bus without pain. In the afternoon he can only walk for seven minutes before he has pain, but if he takes a tablet before starting, pain only comes on after walking for about half an hour.

*Case 7.* M., aged 57. Half a tablet (1/200 gr.) enables him to walk a long way without pain and ensures freedom from pain during fifteen minutes' walk from his house to the station, and a similar distance from the station to his office in the City. Is very liable to anginal attacks when he begins walking after having been at rest. Half a tablet before starting off prevents the onset of this pain.

*Case 8.* M., aged 66. One tablet taken before dressing and undressing keeps him free from pain. Four tablets ensure that he has a comfortable bath, two for the bathing and another two before commencing towelling. When he prevents onset of pain in this way he has no attacks during the twenty-four hours.

*Case 9.* M., aged 70. Takes one tablet before he starts out for a walk and one when he begins to do a little work in the garden. This keeps him free from pain.

*Case 10.* M., aged 45. One tablet prevents pain coming on when he has to walk soon after a meal. After walking for about an hour, or when he is tired, he takes another to prevent onset of attack.

*Case 11.* M., aged 63. One tablet prevents onset of pain on dressing; he takes another before washing, towelling, razor-stropping, and shaving. Two tablets enable him to complete his morning toilet in comfort.

*Case 12.* M., aged 52. Two tablets prevent pain when going upstairs.

*Case 15.* M., aged 58. Onset of pain after walking 300 yards when he takes a tablet, as against 100 yards without a tablet.

*Case 18.* F., aged 59. Finds one tablet a great help because it prevents the pain coming on when she goes out shopping or has to do any special work in the house.

*Case 19.* M., aged 59. If he takes a tablet when leaving the office he is able to walk home without pain.

*Case 20.* F., aged 52. Always pain when cooking the dinner; one tablet allows her to do this in comfort and free from pain.

*Case 21.* M., aged 49. Talking used to make him cry because it brought on the pain; he now can laugh because a tablet beforehand allows him to talk freely in company.

*Case 26.* M., aged 64. One tablet before he goes out of the house enables him to walk for  $1\frac{1}{2}$  to 3 miles without pain. Another tablet prevents pain on defaecation.

*Case 29.* M., aged 56. One tablet prevents the pain coming on for about one hour when walking.

*Case 31.* M., aged 53. One tablet gives him freedom from pain for about two hours' walking.

*Case 32.* M., aged 80. A tablet enables him to walk and climb up steps without getting pain.

*Case 33.* M., aged 55. Has to climb four flights of stairs to his flat, and has to stop every six steps. After one tablet he climbs to the top and only stops once because of breathlessness, but he has no pain.

*Case 34.* F., aged 65. Takes one tablet before she walks out of the house and another on occasions when she gets tired. This ensures that she gets absolute freedom from attacks.

*Case 36.* M., aged 52. A conductor of musical festivals. An occasional tablet enables him to wield the baton enthusiastically.

*Case 37.* M., aged 79. One tablet prevents attacks on going upstairs.

*Case 49.* M., aged 60. Two tablets prevent pain during half an hour's walk.

*Case 53.* M., aged 59. He takes fifteen tablets a week prophylactically, i.e. one tablet each time he walks out; by this means he gets absolute freedom from attacks.

*Case 54.* M., aged 59. Tablet particularly useful to keep away the attacks during the 'rush hours' to and from his work.

*Case 56.* M., aged 57. One tablet prevents the onset of pain when going upstairs or when walking two miles on the level.

*Case 57.* M., aged 60. Always pain on walking for five minutes; one tablet allows him to walk  $1\frac{1}{2}$  hours without pain.

*Case 58.* M., aged 74. Takes a tablet before beginning his morning and evening walks; this entirely prevents pain.

*Case 60.* M., aged 48. Takes a tablet each time before he goes out; previously he was unable to do any walking because of pain.

*Case 61.* M., aged 67. Two tablets enable him to walk  $1\frac{1}{2}$  miles in comfort.

*Case 62.* M., aged 51. As a restaurant manager he is very susceptible to attacks during the 'rush' at the lunch-hour. Two tablets taken separately prevent onset of pain.

*Case 63.* M., aged 51. One tablet before going out in the morning prevents pain coming on during his walk.

*Case 64.* M., aged 53. Always finds that a tablet before starting to walk or work has the effect of preventing pain.

*Case 65.* M., aged 56. Can walk two miles without pain after one tablet, five miles after two tablets taken separately. After taking a tablet he massages a team of footballers, and in spite of strenuous arm exercise he gets no pain. Without tablets he could not attempt to do this.

*Case 71.* M., aged 51. One tablet ensures that he has no pain when he goes for a walk.

*Case 73.* M., aged 46. By using ten tablets a day he reduces the total number of attacks (about twenty daily) to one-half.

APPENDIX. *The Monthly Diary of a Patient with Angina Pectoris, Showing the Details Required of Each Patient in the Series Concerning the Use of Tablets of Glyceryl Trinitrate. (1/100 gr. (0.0006 grm.))*

Date.	Tablets taken to prevent expected attacks.			Tablets taken for the relief of attacks.			Total number of tablets taken during the day.
	7 a.m. to 3 p.m.	3 p.m. to 11 p.m.	Mild attacks or 'warnings'.	Stronger attacks.	Severe attacks.	Nocturnal attacks.	
1933							
July							
17	1.1	1.1	1.1	1		1	9
18	1.1.1.1.1	1.1.1	1.1.1.1.1			1.1	10 $\frac{1}{2}$
19	1.1.1	1.1.1	1.1.1.1.1	1		1.1	10 $\frac{1}{2}$
20	1.1.1	1.1.1	1.1.1.1.1	1		1	10
21	1.1.1	1.1.1	1.1.1.1.1			1	10
22	1.1.1.1	1.1	1.1.1.1.1.1	1		1.1	13 $\frac{1}{2}$
23 S	1.1.1	1.1.1	1.1.1.1.1.1.1.1	1.1		1	12 $\frac{1}{2}$
24	1.1.1	1.1.1	1.1.1.1.1				8
25	1.1.1.1	1.1.1.1	1.1.1.1.1	1		1	9
26	1.1.1.1	1.1.1	1.1.1.1.1			1	9 $\frac{1}{2}$
27	1.1.1.1	1.1.1	1.1.1.1.1	1.1			11
28	1.1	1.1.1.1.1	1.1.1.1			1	14
29	1.1.1.1.1	1.1	1.1.1.1.1			1.1	11 $\frac{1}{2}$
30 S	1.1.1	1.1.1	1.1.1.1.1	1			9
31	1.1.1.1.1	1.1	1.1.1.1.1	1			
Aug.							
1	1.1.1	1.1.1	1.1.1.1.1.1				9
2	1.1.1.1	1.1.1.1	1.1.1.1.1				8 $\frac{1}{2}$
3	1.1.1	1.1.1	1.1.1.1.1			1	9 $\frac{1}{2}$
4	1.1.1	1.1.1	1.1.1.1.1	1			10 $\frac{1}{2}$
5	1.1.1.1.1	1.1	1.1.1.1.1				10 $\frac{1}{2}$
6 S	1	1.1.1.1	1.1.1.1.1				5 $\frac{1}{2}$
7 H	1.1.1.1	1.1	1.1.1.1.1				6
8	1.1.1.1.1	1.1.1	1.1.1.1.1.1			1	11
9	1.1.1.1.1.1	1.1.1	1.1.1.1.1.1			1	10 $\frac{1}{2}$
10	1.1.1.1.1.1	1.1	1.1.1.1.1			1	9
11	1.1.1	1.1.1	1.1.1.1.1			1	11
12	1	1.1.1	1.1.1.1.1			1	8
13 S	1	1.1	1.1.1.1.1			1	8

S = Sunday H = Bank Holiday

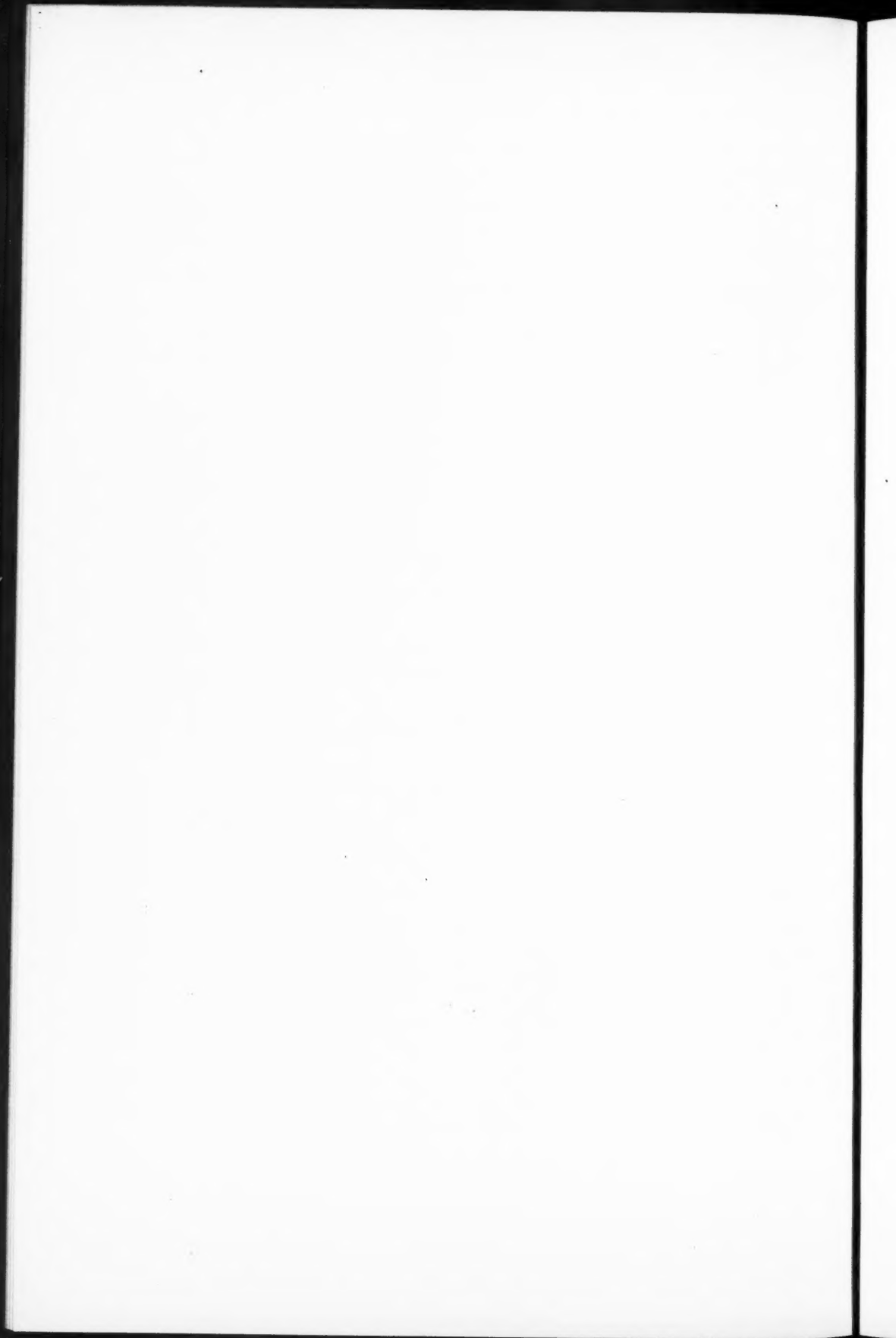
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## INCREASED CARBOHYDRATE TOLERANCE IN DIABETICS FOLLOWING THE HOURLY ADMINISTRATION OF GLUCOSE AND INSULIN OVER LONG PERIODS<sup>1</sup>

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IN treating a large series of patients with diabetes we found that certain cases were difficult to control because wide variations occurred in the level of the blood-sugar when under treatment with insulin. These patients were mostly young subjects with severe diabetes requiring large doses of insulin. Repeated estimations of the blood-sugar in these patients showed wide fluctuations, marked hyperglycaemia being present at certain hours while hypoglycaemia occurred at others. It was thought that this instability of the blood-sugar might be due to a depletion of the hepatic glycogen reserves, thus leading to a diminution of the buffering process of glycogen storage and glycogen break-down commonly regarded as occurring.

In an attempt to increase the glycogen reserves, glucose and insulin were given hourly. The results were surprising, first, in the amount of glucose which severe diabetics could deal with in these circumstances, and secondly, in the marked temporary improvement in carbohydrate tolerance which resulted in some cases. These results are reported in this paper.

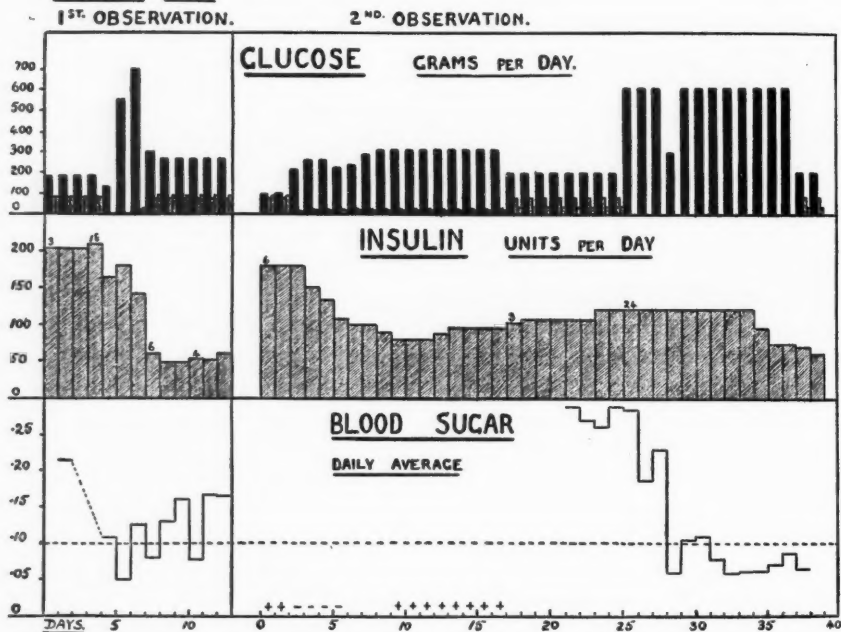
The procedure was as follows. After a few days' observation in hospital on diet and insulin, the patients were kept in bed, and all food except glucose withheld. Anhydrous glucose dissolved in a few ounces of water and flavoured with a slice of lemon was then given hourly during the day and night in doses of from 10 to 30 grm. Insulin was given subcutaneously hourly throughout the twenty-four hours in doses of 1 to 10 units. Blood-sugar estimations on capillary blood obtained by finger puncture were made at hourly or at two-hourly intervals during the whole period of observation, using the Folin-Wu micro technique. The period of glucose administration varied in different patients from two to sixteen days.

The results obtained are demonstrated in the charts. It will be seen that they vary from a very striking improvement in carbohydrate tolerance in Cases 1 and 2 to a relatively slight change in Cases 5 and 6. In these charts the solid black lines represent the glucose equivalent of the diet (calculated glucose yield from carbohydrate, protein, and fat), the accompanying stippled

<sup>1</sup> Received November 3, 1933.

columns the protein and fat. When the stippled columns are omitted, this indicates that glucose only was being given, and the solid black column then represents glucose ingested as such. The obliquely hatched columns represent insulin in units per day, the figure at the top of the column indicating the number of injections in which it was given; thus the figure 3 indicates three injections, which were usually given at 6 a.m., 2 p.m., and 10 p.m., while the figure 24 means that the injections were hourly. The curve showing the level of the blood-sugar was made by recording a daily figure which is the average of the blood-sugar estimations for that day; in most instances this figure represents the average of twenty-four estimations made at hourly intervals, but in the later stages of observation and in the preliminary observation period the number of estimations was often smaller.

### CASE I. G.S.



Case 1. G. S. Reg. No. 41620/31.

A girl aged 16 years with two-and-a-half years' history of diabetes. This patient had been attending hospital under Dr. Leyton for some eighteen months, during which time her insulin dosage had had to be steadily increased from 50 units daily in 1930 to 204 units daily at the time when these observations were begun. At this time she had been in hospital for two-and-a-half months, during which time she had been continually unbalanced with hyperglycaemia and hypoglycaemia, frequently accompanied by reactions, occurring at different times in the same day. She was passing considerable amounts of sugar in the urine, and there was continuous well-marked ketonuria.

*First period of observation*: Chart 1, left-hand segment. (3 Jan. to 15 Jan., 1932.)

The patient was on a diet of C 120, P 86, F 84, with a glucose equivalent of 178 gm., and was receiving insulin  $3 \times 68 = 204$  units daily. Glucose administration was begun at 2 p.m. on 7 Jan. (the fifth day of observation shown in Chart 1), and continued till 11 a.m. on 9 Jan.; it was given in hourly doses of 10 to 50 gm. Insulin was given 10 units hourly with the exception of certain hours during the night and occasions when the blood-sugar was low, when it was omitted; it will be seen that the total insulin dosage during this period was lower than that previously given. When glucose administration ceased she was put on a diet containing about the same protein and fat as she was receiving at the beginning of the experiment but with more carbohydrate. Her insulin requirement was 50 units daily as compared with the previous 204 units. This improvement was not maintained and the patient was soon as she had been before glucose administration.

*Second period of observation*: Chart 1, right-hand segment. (24 March to 3 May, 1932.)

This was begun two months after the first observation. In the weeks preceding glucose administration the patient had been on a high carbohydrate, low protein, low fat diet, C 300, P 24, F 9, with a glucose equivalent of 314 gm. On this her insulin requirement had diminished from 180 units daily to between 80 and 110 units daily. In the eight days immediately preceding the glucose administration the patient's diet had been C 151, P 74, F 35, with a glucose equivalent of 196, and the insulin dosage 110 to 120 units daily. That the insulin was obviously inadequate is shown by the blood-sugar which was ranging from 0.4 to 0.15 with an average of 0.25 gm. per cent.

Tests for ketonuria were made each day throughout the period of observation and, except for occasional traces, were consistently negative except on the two days immediately preceding glucose administration. For many weeks the diet had been extremely low in fat.

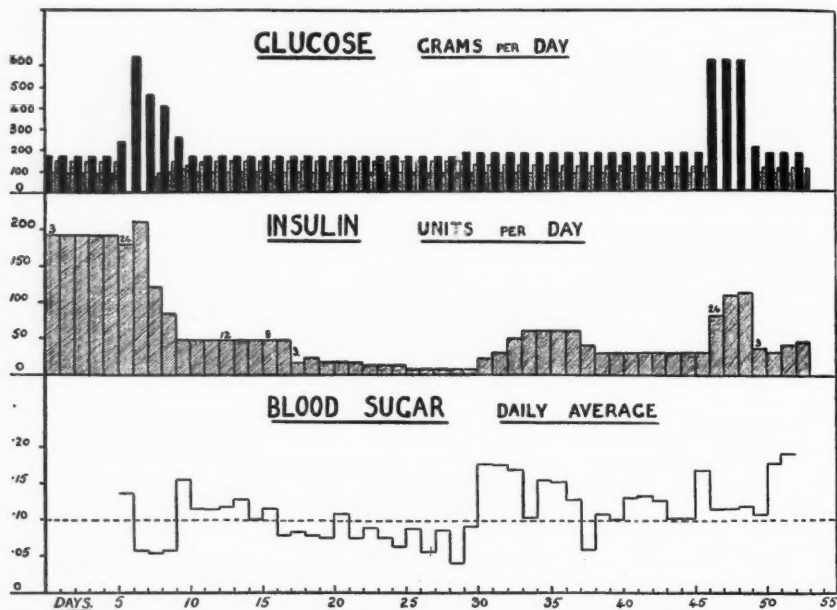
From 19 April to 30 April, a period of twelve days, the patient was then given nothing but glucose, 25 gm. every hour, or a total of 600 gm. daily, except on April 22 when only half this amount was given. Insulin was given hourly in 5-unit doses, a total of 120 units daily or the same daily total as before. As will be seen by the curve, the blood-sugar gradually fell, until on the eighth day of glucose administration the patient was profoundly hypoglycaemic with an *average* blood-sugar of 0.06 per cent. The insulin was then reduced to 4 units hourly, and the following day to 3 units hourly, without any material rise in the blood-sugar occurring. It will be seen that steady improvement had occurred during the period of the régime, so that while at the beginning hyperglycaemia was present with 5 units of insulin hourly, at the end there was constant hypoglycaemia with only 3 units of insulin hourly.

The improvement was not maintained; when the patient was put on a regular diet her condition soon reverted to that present before glucose administration. She is now (April 1933) on a diet of C 159, P 64, F 44, and is receiving  $3 \times 30$  units of insulin. She is well and free from symptoms but is hyperglycaemic during parts of the day and passes large amounts of sugar in the urine.

Case 2: P. S. Reg. No. 30047/32. (Chart 2, 11 Jan. to 3 March, 1932.)

A boy aged 17 with a four years' history of diabetes, of which the last two had been spent as a laboratory attendant in the London Hospital; during this period he had been under close observation. The insulin dosage had had to be steadily increased from 40 and later 60 units in 1930, to 120 units in 1931, and 192 units in 1932. On this amount of insulin his blood-sugar showed wide fluctuations throughout the day, varying from marked hyperglycaemia to hypoglycaemia at different times of the same day. There was moderate ketonuria.

### CASE 2. P.S.



In the period immediately preceding glucose administration this patient was having a diet of C 101, P 98, F 146, with a glucose equivalent of 172 gm. He was receiving  $3 \times 64 = 192$  units of insulin. He was then given glucose and insulin hourly for four days, fat and protein being given in addition on the third and fourth day. On the sixth day he returned to the same diet that was being given before glucose administration. On the first day he took approximately 10 gm. of glucose hourly, a total of 240 gm., on the second day approximately 25 gm. of glucose hourly, a total of 618 gm., on the third day 458 gm., and on the fourth day 413 gm. The insulin dosage on the first two days was approximately 10 units an hour, 180 units on the first day, 210 units on the second. The total insulin administered was therefore practically the same as before glucose administration. The blood-sugar fell steadily and the patient became consistently hypoglycaemic on the second, third, and fourth days, the *average* blood-sugar being between 0.05 and 0.06 per cent.

The insulin dosage was gradually reduced so that by the fifth day the patient was receiving only 2 units hourly, or a total of 48 units. On the

sixth day following glucose administration, or the eleventh day of observation, the patient was thus taking the same diet as before glucose administration, but was requiring only 48 units of insulin, whereas 192 units had previously failed to control him. The total dosage was kept constant for a further seven days, but the frequency of injection was reduced to two-hourly on the eighth day, and three-hourly on the eleventh day. On this day a further improvement in tolerance occurred and the patient again became consistently hypoglycaemic. The frequency of insulin administration was reduced to thrice daily, and the dosage steadily reduced until on the twenty-first day after beginning glucose, or the twenty-sixth day of observation, the patient was receiving only  $3 \times 3 = 9$  units daily. In spite of this great reduction of insulin, the *average* blood-sugar remained below normal levels. This continued for five days and then the patient developed a cold in the head with fever and labial herpes; his blood-sugar rose and his insulin requirement increased and never again approached this low level. On the forty-second day after glucose administration, or the forty-seventh day of observation, a three-day period of hourly glucose and insulin administration was repeated. No improvement in tolerance followed this second glucose-insulin régime.

The temporary improvement in this patient following the first administration of glucose was the most marked we have seen, the patient being hypoglycaemic over a five-day period on a dosage of  $3 \times 3 = 9$  units of insulin, whereas on the same diet before glucose he had been uncontrolled on  $3 \times 68 = 192$  units. The subsequent course of this patient has been a return to his previous condition. He has now passed out of my care, but when seen some months ago he said that he was taking large doses of insulin, was feeling fairly well, and was having occasional reactions.

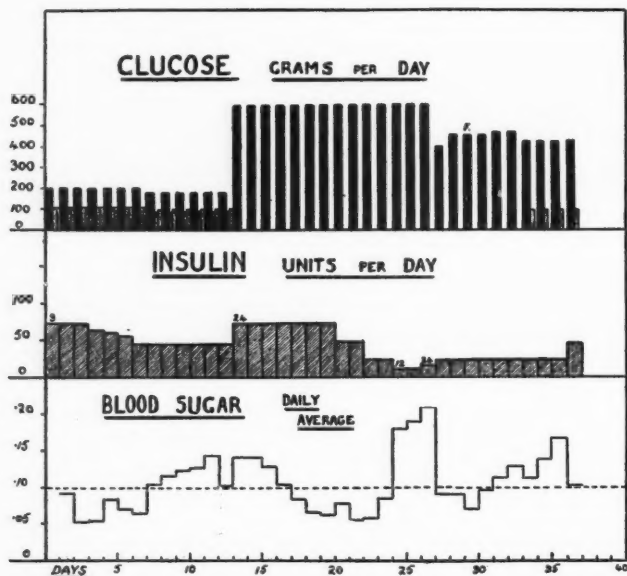
*Case 3: L. C. Reg. No. 30467/32. (Chart 3, 26 March to 1 May, 1932.)*

A boy of 13 years with a four years' history of diabetes, who had been for three years under observation at the London Hospital. His insulin had been increased from 20 units in 1929 to 70 units in 1930 and had then remained at about that level. At the beginning of the period of observation on 26 March the patient was receiving a diet of C 120, P 105, F 105, with a glucose equivalent of 191 gm. He was having  $3 \times 25 = 75$  units of insulin daily and was well controlled, the average blood-sugar being well below normal. There was no ketonuria. His diet and insulin were then adjusted so that he should have an insulin dosage which was insufficient. This was achieved with a diet of C 120, P 80, F 90, having a glucose equivalent of 172 gm., and an insulin dosage of  $3 \times 15 = 45$  units daily; on this he remained for six days during which period the average daily blood-sugar was, with one exception, above normal; there was no ketonuria.

Glucose administration was begun on April 8 on the fourteenth day of observation, 25 gm. being given hourly, or a total of 600 gm. in the twenty-four hours; this was continued until 21 April, that is, for a continuous period of fourteen days. Insulin was administered 3 units hourly. As will be seen from the Chart the daily average blood-sugar steadily fell and reached 0.06 per cent. on the twentieth day of observation, i.e. on the seventh day of glucose administration. The insulin was then reduced to 2 units per hour for two days and then to 1 unit per hour for two days, the average blood-sugar remaining below normal. It will be seen that during this eleven-day period of continuous glucose administration a steady improvement had occurred enabling a 66 per cent. reduction in the amount of insulin required.

On the twenty-fifth day of observation the insulin was further reduced to 1 unit two-hourly. This proved insufficient, and the blood-sugar rapidly rose to above normal. The insulin was therefore increased to 1 unit hourly on the twenty-seventh day, and the glucose reduced to 480 gm. daily. Fat to the equivalent of that present in the diet before glucose administration was added on the thirtieth day as indicated by the letter F in the chart, and protein on the thirty-fourth day, glucose equal to their glucose equivalent being in each case deducted. A rise in the daily average blood-sugar occurred on the addition of fat and a more marked rise when protein was added.

### CASE 3. L.C.



When a regular diet was resumed, this patient's condition gradually returned to that present before glucose administration. He is now on a diet of C 148, P 73, F 96, and is taking  $2 \times 30 = 60$  units of insulin daily. He is well and working regularly.

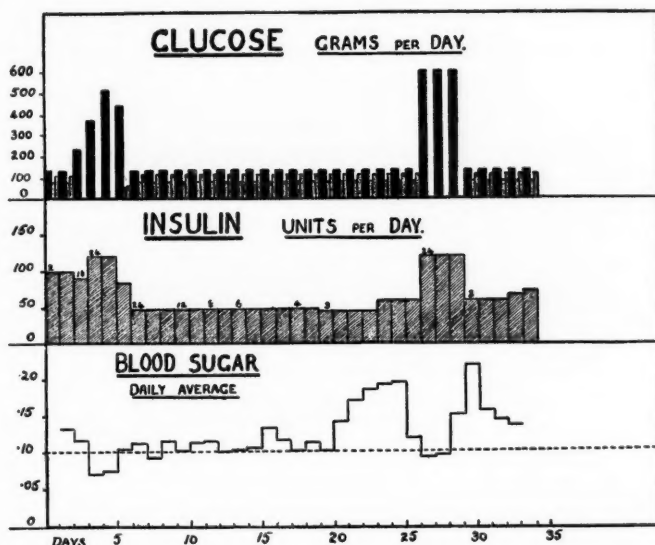
Case 4: R. C. Reg. No. 30214/32. (Chart 4, 7 Feb. to 11 March, 1932.)

A boy aged 17 with six years' history of diabetes, who had been under observation at the London Hospital during the whole of that period. His insulin dosage had been 8 units per diem in 1926 and 1927. In 1928 he got progressively worse and his insulin was increased to 70 units per diem, at which it remained during 1929. In 1930 the insulin was increased to 100 units daily, and there it remained when the observations were begun in February 1932.

At this time he was on a diet of C 75, P 86, F 116, with a glucose equivalent of 136 gm., and insulin  $2 \times 50 = 100$  units daily. The twenty-four hours' urine showed some glycosuria and occasional slight ketonuria. On the third day of observation the administration of glucose and insulin hourly was begun and continued over a four-day period, 235 gm. of glucose being given on the third, 370 gm. on the fourth, 510 gm. on the fifth, and

440 grm. on the sixth day of observation. The previous diet was then resumed. Insulin was given 5 units hourly for the first three days of glucose administration, and then gradually reduced to reach 2 units hourly on the seventh day of observation. It will be seen that the improvement in carbohydrate tolerance following glucose administration was less than that in the three patients previously described; on the same diet as before glucose

#### CASE 4. R.C.



administration the amount of insulin required was halved. Both diet and insulin were now kept constant, and the number of insulin injections gradually diminished. No effect was noticed until the number of injections was reduced to 3 on the nineteenth day. On the following day the average blood-sugar rose well above normal. This rise of blood-sugar was associated with the development of a 'cold', and it seems probable that the diminished carbohydrate tolerance was due to this factor rather than to the reduction in the number of insulin doses. The deteriorating influence of such infections in diabetes is well recognized, and has been rather strikingly demonstrated in this series on several occasions. On the twenty-third day the insulin dosage was increased to  $3 \times 20 = 60$  units daily, and a marked fall in the average blood-sugar occurred on the twenty-fourth day.

On the twenty-fifth day a second course of glucose administration was begun and continued over a three-day period. No improvement followed the second glucose administration.

This patient was last seen on 22 Feb., 1933. He is still on the same diet as he was receiving at the time of observation. He now has 70 units of insulin daily as against 100 units at that time.

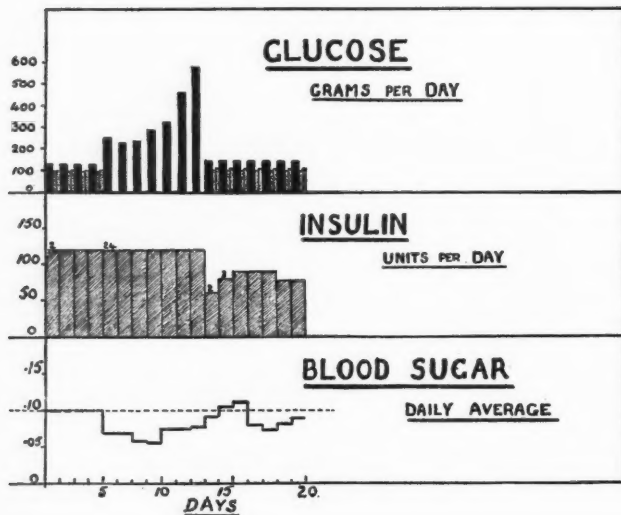
Case 5: V. G. Reg. No. 30361/32. (Chart 5, 6 March to 23 March, 1932.)

A man aged 26 with five years' history of diabetes, who had been under observation at the London Hospital during the whole of that period. He

had also a moderately extensive pulmonary tuberculosis. This patient was older than any of the previously described patients and his diabetes was under better control. He had required 30 units of insulin in 1927 and this dose had had to be gradually increased until 1930 when he was receiving 120 units. Since that time his insulin requirement had remained at that level.

When the observation was begun he was receiving a diet of C 63, P 103,

### CASE 5. V.C.



F 106, with a glucose equivalent of 138 grm., and  $2 \times 60 = 120$  units of insulin daily. Glucose and insulin hourly were begun on the fifth day, and the amount of glucose gradually increased to reach 600 grm. on the twelfth day. During the period of glucose administration the blood-sugar remained at a low level, but little improvement in the insulin requirement resulted. He was last seen in Feb. 1933; he was then taking the same diet as before glucose administration and 80 units of insulin daily.

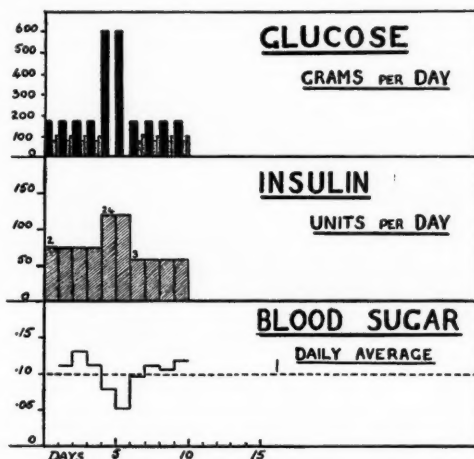
Case 6: F. W. Reg. No. 40464/32. (Chart 6, 26 March to 4 April, 1932.)

A woman aged 42 who had been under observation at the London Hospital for nine years. Her insulin requirement had gradually risen until 1928, since which time it had been between 70 and 80 units daily.

At the time of these observations she was on a diet of C 119, P 81, F 92, with a glucose equivalent of 174 grm., and insulin  $2 \times 38 = 76$  units daily. Hourly insulin and glucose were begun on the fifth day and continued for forty-eight hours, the patient receiving 25 grm. of glucose and 5 units of insulin hourly. The average blood-sugar fell well below normal during the period of glucose administration, but no improvement in insulin requirement resulted. It will be noted that this patient and the preceding one, in whom also little or no improvement followed the use of glucose, were both older individuals in a state of satisfactory carbohydrate-insulin balance. This

patient was last seen in Jan. 1933 when she was taking the same diet and insulin as before observation.

### CASE 6. F.W.



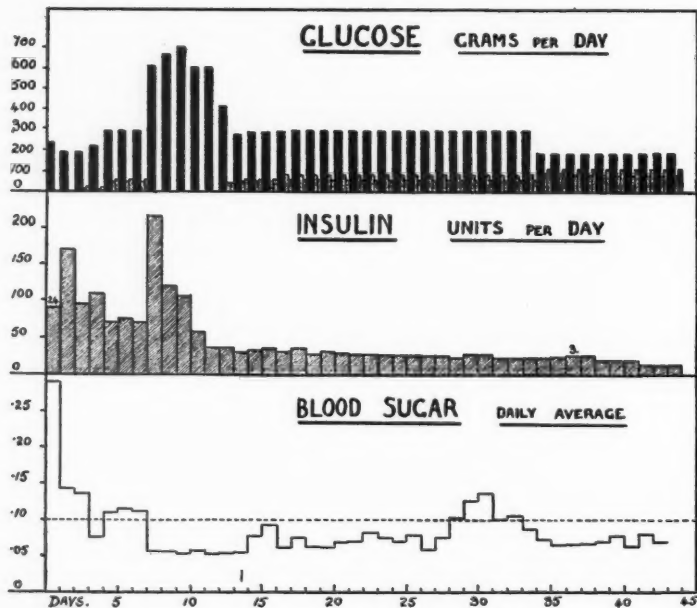
Case 7: R. G. Reg. No. 30228/32. (Chart 7, 10 Feb. to 24 March, 1932.)

This boy aged 10 was admitted to the London Hospital in a state of incipient coma. He gave a history of the acute onset ten days previously of diabetic symptoms; his mother's sister and both maternal grandparents had died of diabetes. He was treated with glucose and insulin from the time of admission, but received small amounts of additional food on the third, fourth, fifth, sixth, and seventh days of observation. His condition by then was so much improved that it was considered feasible to omit other food and to give him glucose alone and insulin over the whole twenty-four hours. This was begun on the eighth day of observation when he was given from 25 to 30 gm. of glucose hourly, a total of 620 gm. in the twenty-four hours, and insulin 10 units hourly. He gradually became hypoglycaemic, and on the two following days the glucose was increased and the insulin diminished without any rise occurring in the blood-sugar. Thus on the ninth day he had 660 gm. of glucose and 120 units of insulin or 5 units hourly, on the tenth day 700 gm. glucose and 105 units of insulin, the average blood-sugar remaining in the neighbourhood of 0.05 gm. per cent. On the eleventh and twelfth days the glucose was held constant at 25 gm. hourly, a total of 600 gm., and the insulin further reduced to 58 units on the eleventh day and 36 units or 1.5 units hourly on the twelfth day. From the thirteenth day onward glucose administration was reduced and increasing amounts of other food added, so that by the twentieth day glucose was entirely discontinued, the patient being then on a diet of C 232, P 86, F 64, with a glucose equivalent of 288 gm. On this he remained until the thirty-fourth day, when the diet was reduced to C 117, P 87, F 109, with a glucose equivalent of 178 gm. His insulin was gradually reduced to 1 unit hourly, an occasional dose of 2 units being given if the blood-sugar showed signs of rising. On the thirty-seventh day the number of insulin injections was reduced to  $3 \times 8 = 24$  units daily; and this was further reduced on the

thirty-ninth day to  $3 \times 6 = 18$  units and on the forty-second day to  $3 \times 4 = 12$  units, the average blood-sugar still remaining below normal.

He was discharged from hospital on 27 March, 1932, on this diet and  $3 \times 4$  units insulin. On 5 July, 1932, the insulin was reduced to  $2 \times 4$  units daily. Since discharge he has been seen at fortnightly intervals. He has remained well, has grown  $1\frac{1}{4}$  in. and has gained 11 lb. in weight. The

### CASE 7. R.G.



urine has been free from sugar at each examination. On 28 Feb., 1933, his diet was increased to C 151, P 100, F 110, as he was having symptoms suggesting hypoglycaemia. On 16 March, 1933, he was admitted for investigation as to his present condition. The blood-sugar was then examined two-hourly, day and night, over a period of five days. It varied from a maximum of 0.13 to a minimum of 0.06, the average blood-sugar for each of the five days being 0.08, 0.09, 0.08, 0.08, and 0.08. Insulin was then discontinued, and his blood-sugar followed two-hourly for a further three days. It showed a maximum of 0.13 and a minimum of 0.06, the average blood-sugar being 0.098, 0.097, and 0.093. A sugar tolerance test was made on the fifth day following the omission of insulin. The following are the blood-sugar percentages at the time of giving 50 grm. of glucose and at half-hourly intervals afterwards 0.054, 0.058, 0.153, 0.2, 0.166, 0.142, 0.07, 0.058, 0.066, 0.057, 0.064, 0.047.

Specimens of urine were collected every half hour during the test, none showed any reduction of Benedict's reagent.

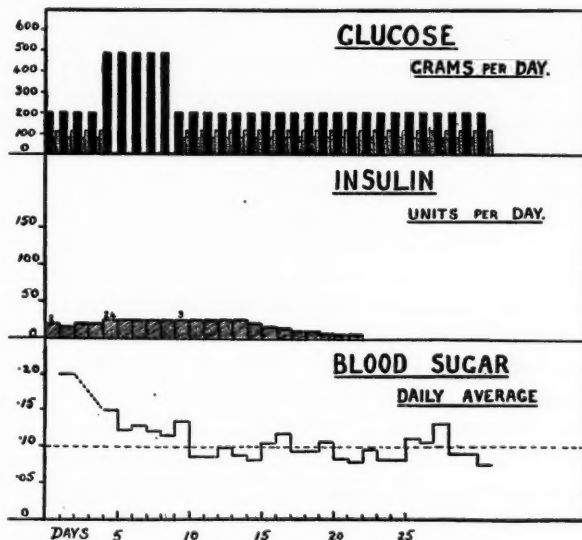
It will be seen that though the blood-sugar reached the somewhat high figure of 0.2 one-and-a-half hours after glucose, it had returned to below normal at the end of three hours, while at the end of five hours there was

definite hypoglycaemia. In our experience cases like this with sudden onset in young children usually run a severe course. The results of treatment in this boy seem therefore very satisfactory.

Case 8: C. C. Reg. No. 30609/33.

A man aged 44 with a history of diabetic symptoms of two months' duration. He had received dietetic treatment for one month before admission.

### CASE 8. C.C.



There was no ketosis. On admission he was put on a diet of C 122, P 79, F 102; no insulin was given. A sugar tolerance test gave the following percentages of blood-sugar at the time of the administration of 50 grm. of glucose and at half-hourly intervals afterwards: 0.103, 0.22, 0.25, 0.22, 0.2, 0.2, 0.2.

After a three-day period of observation his diet was slightly altered to C 153, P 74, F 111, with a glucose equivalent of 204, and insulin  $2 \times 10 = 20$  units daily was given. On this regimen he became sugar-free in four days. Food was then discontinued, and glucose 20 grm. hourly and insulin 1 unit hourly were given for five days. The average blood-sugar remained above the normal level during the period of glucose administration. He was then put back on the same diet and insulin  $3 \times 8 = 24$  units daily given. On the tenth day following the beginning of glucose administration, that is, on the fourteenth day of observation shown in the chart, a severe hypoglycaemic reaction occurred. The insulin was successively reduced on subsequent days, until on the twenty-third day of observation it was entirely omitted. In spite of this the patient's average blood-sugar remained usually below normal. A sugar tolerance test carried out on the twenty-seventh day of observation gave the following percentages of blood-sugar at the time of giving 50 grm. of glucose and at half-hourly intervals after: 0.117, 0.16, 0.16, 0.15, 0.09, 0.10, 0.07, 0.06, 0.07, 0.08, 0.07.

This patient has since remained sugar-free and without symptoms. He was last seen on 17 Oct., 1933, that is, five months after discharge from hospital. There was no sugar in the urine, and the blood-sugar was within normal limits.

A number of other cases have been treated with three- or four-day periods of hourly insulin and glucose. They have shown in general similar results to those here reported. It has not seemed necessary therefore to include their details.

#### *Summary of Case Reports*

It will be seen that in the eight cases reported there occurred, with one exception, either during or following the period of glucose administration a definite improvement in carbohydrate tolerance. This improvement was shown by a diminution in the amount of insulin required to keep the blood-sugar normal or subnormal. In the older and better adjusted patients the improvement while definite was much less striking than in the younger ill-adjusted patients, in some of whom the improvement was dramatic. The improvement appeared within a few hours of commencing glucose and was a progressive process. There was some evidence that the process of recovery in its most complete form took about twelve days to develop. Thus in Case I, in which at the second observation glucose administration was continued for twelve days, the insulin dosage was steadily reduced from the tenth to fourteenth days from the date of commencement; in Case 3 the insulin dosage was reduced from the eighth to the eleventh day of glucose administration, when further reduction proved impracticable. In Case 2 large amounts of glucose were given only for three days and glucose without other food on two days only; following the first improvement, which began at once, a second period of improvement set in twelve days after beginning the glucose, or nine days after its discontinuance. This second period of improvement was progressive and persisted for a further thirteen days. With the exception of Cases 7 and 8, the improvement which followed glucose administration was only temporary. These were both early cases with only a short history of diabetic symptoms. The subsequent history of the remaining patients does not suggest that they were permanently either benefited or harmed by the treatment. In some milder cases of diabetes which we have more recently treated in this way, but which are not included in this series, a permanent improvement has appeared to occur. It is interesting that in the two patients to whom a second course of glucose was given, during their period of improved carbohydrate tolerance, no further improvement resulted (Cases 2 and 4). This observation would seem to be important in considering any theory of the method of action of glucose in these cases.

The quantity of glucose given to these patients is greater than in any previous observations on diabetes known to us. It approximated 25 gm. an hour, or 600 gm. daily. We were surprised to find that these amounts of glucose were tolerated with an insulin dosage little or no greater than that

required with an ordinary restricted diabetic diet; and that under these conditions the patient was usually continuously hypoglycaemic throughout the twenty-four hours. A further point of interest in these observations was the complete absence of hypoglycaemic symptoms. Even though the blood-sugar remained over a period of hours below the point at which quantitative readings were possible, symptoms rarely occurred.

### *Discussion*

The results of these observations seem to be of some theoretical interest. What is the meaning of this diminished insulin requirement of severe diabetics during and following a glucose-insulin régime? We do not consider that we have sufficient evidence to indicate an answer to this question, but some discussion of possible explanations appears advisable in view of the somewhat unsatisfactory theories as to the nature of diabetes at present in vogue, and the obvious difficulty of reconciling the observations reported in this paper with the theory of pancreatic exhaustion.

The normal response to the ingestion of sugar is generally held to be increased insulin production. This is the common interpretation of the well-known fact that following a sugar tolerance test the blood-sugar frequently falls to a level below that present before sugar was given. Several observers have reported the occurrence even of hypoglycaemic symptoms following sugar tolerance tests. Most of these observations have been on normal subjects or non-diabetic patients, but similar falls in blood-sugar following ingestion of glucose do sometimes occur in patients with diabetes. Thus Ralli and Shannon (1) studied the blood-sugar over a five-hour period following the administration of 100 grm. of glucose. They do not comment on the fact, but their tables show that the blood-sugar at the end of the five-hour period was lower than the fasting blood-sugar taken immediately before giving glucose in 5 out of 6 normals, 5 out of 6 mild diabetics, 4 out of 6 moderately severe diabetics, and 0 out of 8 severe diabetics. These results of sugar tolerance tests represent the response to a single ingestion of sugar. Observations on the response to repeated ingestions have also been made. Thus Hamman and Hirschmann (2) showed that a second ingestion of glucose caused a less marked hyperglycaemia than the first in both normal and diabetic subjects. Similar observations have been made by Lennox (3) who tested the effect of a second dose of sugar in normal and epileptic subjects. The sugar was given by the mouth in some experiments, intravenously in others. Lennox found that a second ingestion of sugar, if largish amounts were used, produced much less rise in the blood-sugar than did the first. The same difference was seen with injections, but here it was much less marked. Perhaps the most interesting observation is that of Thalhimer and his co-workers (4). They gave four normal subjects a slow uniform intravenous injection of 10 per cent. glucose, at the rate of 0.9 grm. glucose per kilogram of body-weight per hour, over about a two-hour period. There was a gradual

rise in the blood-sugar level during the first hour, but during the second hour the blood-sugar instead of increasing declined. Following the injection the blood-sugar went to a low level and there were hypoglycaemic symptoms like those seen in moderately severe insulin shock.

The customary explanation of this secondary hypoglycaemia is stimulation of the islands of Langerhans by the previously raised blood-sugar, the regulatory mechanism of blood-sugar level being regarded as insulin stimulation by hyperglycaemia, and the stimulation of glycogen break-down, either directly or through the suprarenals, when hypoglycaemia occurs. It will be seen that most of these observations of apparent increased insulin production following the administration of glucose have been made in normal subjects or in mild diabetics. In these this explanation is adequate.

This hypothesis, however, will not explain the observations recorded in this paper. In our patients a more or less persistent hyperglycaemia had been present for some time before treatment with glucose was instituted; and the improvement associated with the treatment occurred in all instances during periods of persistent hypoglycaemia often of extreme degree. The improvement which followed the ingestion of sugar in these cases cannot therefore be due to an increased secretion of insulin due to raising of the blood-sugar. If the ingestion of sugar did lead, in these patients, to direct stimulation of insulin production we must suppose that sugar presented by mouth acts differently, in this respect, from sugar already circulating in the blood stream. These observations do, we think, suggest such a possibility.

There may of course be chemical differences between glucose as absorbed from the gut and that shed into the blood from the liver, but all attempts to demonstrate such differences have so far failed. It has also been suggested that the absorbed glucose is in some way altered in the liver, so that it is rendered more easily available for final oxidation. But the circulating blood-sugar also passes through the liver; it is difficult to see why the one should be affected and the other not. It would seem that the difference in effect of absorbed sugar from circulating sugar, should it really exist, must lie farther back in the stage of its absorption from the intestinal canal: the absorption of glucose must somehow stimulate the pancreas. Macallum (5) in 1929 postulated the presence of an insular hormone in the duodenum, the production of which is caused by the presence of sugar in the intestine. More recently Laughton and Macallum (6), in reporting observations carried out on a large series of animals, claimed to have isolated from the duodenal mucosa of rabbits, dogs, hogs, and cattle, an active preparation which diminishes experimental hyperglycaemia in normal and partially depancreatized animals but has no effect on the hyperglycaemia of totally depancreatized dogs. They consider the probable mode of action of their preparation to be a stimulation of the islands of Langerhans to secrete insulin. If the improvement in our patients was due to increased secretion of insulin, our results could be explained by their theory.

It must be emphasized, however, that we have no direct evidence of

increased insulin production, and that the diminished insulin requirement observed in our patients may be due not to an increased secretion of insulin by the patient, but to an increased efficiency of the administered or secreted insulin. A number of ways in which such an increased efficiency of insulin might have been brought about at once suggest themselves.

It is, for instance, generally believed that carbohydrates are better tolerated when the glycogen reserves of the body are full than when they are empty. A glucose tolerance test results in a higher degree of hyperglycaemia following a prolonged fast than after liberal carbohydrate feeding during the preceding days (7). This was the conception on which our experiments were based. The results obtained in some of these observations were, however, on such a scale that this explanation seems inadequate. The delayed improvement which occurred in some cases is also difficult to explain on this basis. Recent work (8) has indeed thrown doubt on the whole assumption of diminished glycogen stores in diabetes. The lack of improvement following a second course of glucose in Cases 2 and 4 would, however, be a point in favour of this theory.

It might again be argued that the improvement noted in these cases was due to the increased frequency of insulin administration. We have made one or two observations in which hourly insulin without glucose was given. These observations did indicate an increased efficiency with frequent injections, but no improvement like that seen with glucose occurred. Dr. Marrack kindly examined the urine from one of these patients while receiving infrequent large doses of insulin; he was unable to obtain any yield of insulin from the urine either by Collip's or by the picrate method. Ueberrack and Zell (9) also examined the urine in a patient of this type similarly treated, and failed to demonstrate any excretion of insulin in the urine although added insulin was recovered quantitatively from normal urine by these methods.

Another suggestion is that the improvement in our patients was due to the elimination of ketosis which is known to interfere with insulin activity. Quantitative determinations of ketone bodies were not carried out, but daily qualitative tests with Rothera's and Gerhardt's reagents were made on a twenty-four hour specimen of urine on each day of observation in every case. These showed that ketosis was present in some, but not in all, of the patients and that well-marked improvement occurred when ketonuria was absent or slight in the period preceding glucose administration. Thus in Case 3 no ketonuria was present. In Case 4 only a weakly positive Rothera reaction was occasionally found. In Case 1 moderate ketonuria was present at the beginning of the first observation, but during the whole of the second period of observation ketonuria was present only on the two days immediately preceding the administration of glucose, and the diet for three weeks before glucose administration had been extremely low in fat. There was no ketonuria in Cases 5, 6, and 8. These observations suggest that removal of ketosis is not the explanation of the improvement which followed glucose administration.

Himsworth (10) considers that insulin, as we know it and as it is secreted by the pancreas, is an inactive material which requires activation by some unknown substance for which he suggests the name of insulin kinase. He thinks this insulin kinase is produced in the liver. Himsworth has also been impressed by the favourable results of glucose and insulin administration. Our observations might be explained by increased 'activation' of insulin. There is, however, no direct evidence in these observations to support this hypothesis.

Whatever may be the explanation of the phenomena described in this paper—and it is clear that we have no adequate explanation—it is at least obvious that our findings are difficult to reconcile with the generally accepted theory of pancreatic 'exhaustion' as the important factor in diabetes. Case 3, a boy of 13 with severe diabetes, was given 500 to 600 grm. of glucose daily over a twenty-day period. He utilized this glucose on a dosage of insulin only slightly greater than that adequate to control him on a restricted diabetic diet, and showed continuous improvement over the first twelve days. At the end of twelve days on 600 grm. of glucose daily his insulin requirement was only one-third of the requirement at the beginning. In no case have we seen any evidence of exacerbation of diabetes follow these large doses of glucose. All but one of the patients have now been observed for a period of more than one year following the use of glucose.

It is further obvious that these observations are in accord with the favourable results obtained with the relatively high carbohydrate diets which have recently become increasingly popular in the treatment of diabetes, and that they offer additional evidence in support of their use.

In diabetic coma, the use of hourly insulin and glucose is now with us a routine. In these cases the first doses of insulin must be large, e.g. 50 units, and should be given intravenously.

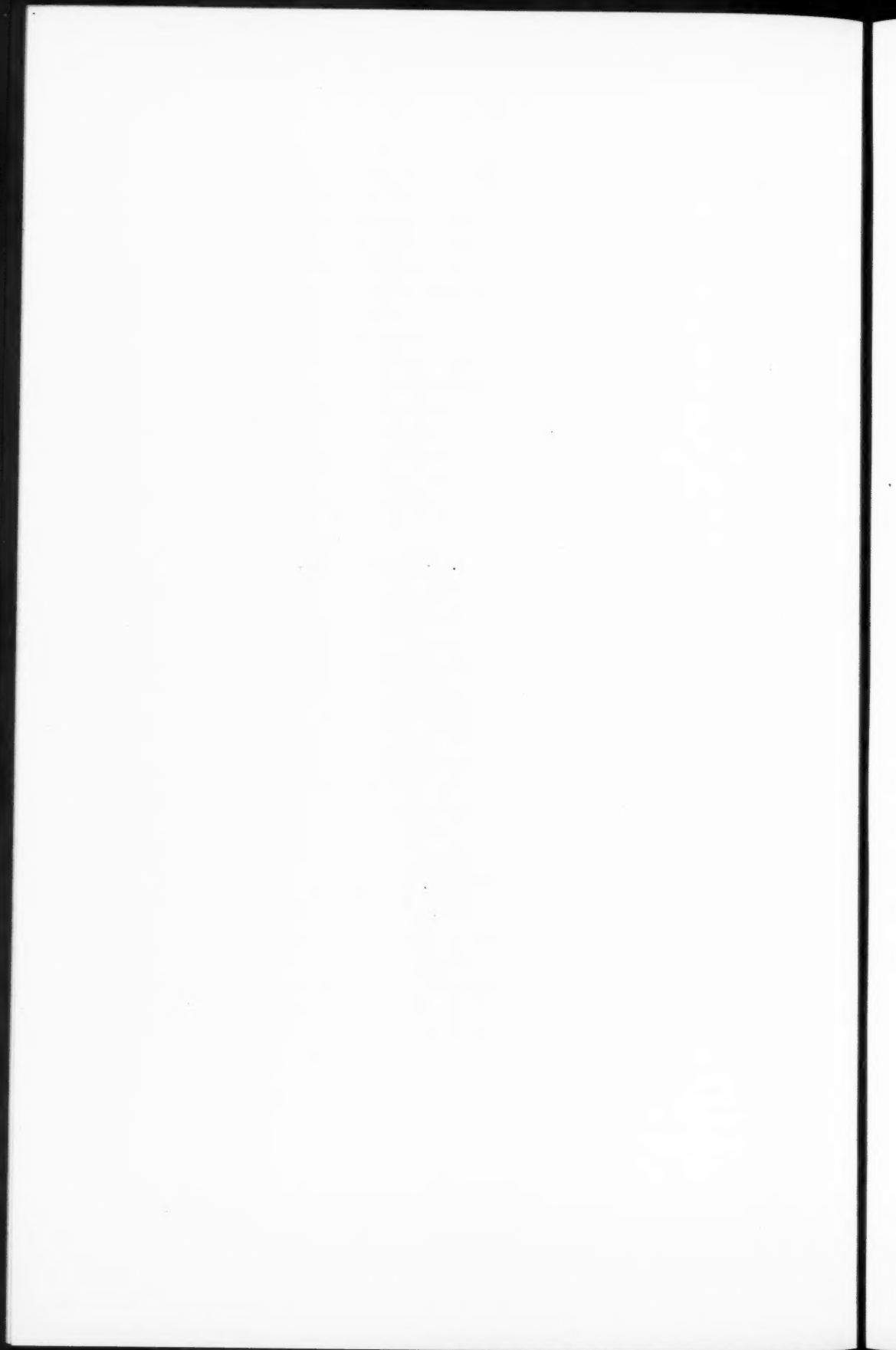
### *Summary*

A number of severe cases of diabetes have been given glucose and insulin hourly without other food over periods of days. Given in this way large amounts of glucose, 600 grm. daily, are well tolerated by severe diabetics, the insulin required being no greater than that necessary on an ordinary restricted diabetic diet. During and following such administrations of glucose marked temporary improvement in carbohydrate tolerance, with great reduction in the amount of insulin required, sometimes occurs. In the most marked instance in this series the reduction of insulin was from 192 units daily before glucose to 9 units daily on the twenty-first day after glucose administration, the diet being unchanged. The explanation of this improvement is not known. The possible bearing of these observations on theories of the pathogenesis of diabetes is discussed.

My most grateful acknowledgements are due first to Miss Rose Simmonds, Sister to the Diabetic Ward, without whose enthusiasm, care, and skill in the management of patients these observations would never have been made. To her, and to the nurses associated with her, I am also deeply indebted for the hundreds of blood-sugar estimations made in the course of these observations. My thanks are due to Dr. Leyton for allowing me to take over Case 1, a patient whom he had been following for many years. I should like also to express my gratitude to my late House Physician, Mr. Clifford Wilson, for his care and skill in the preparation of the charts embodied in this paper; to him I am also greatly indebted for assistance in the conduct of the observations.

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## A CONTRIBUTION TO THE STUDY OF ERYTHROBLASTOSIS: ICTERUS GRAVIS NEONATORUM<sup>1</sup>

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With Plates 12 to 16

THE following communication is based upon the clinical and pathological study of eighteen cases of icterus gravis neonatorum, carried out at the Hospital for Sick Children, Great Ormond Street. Eleven were investigated personally, and of these eight came to autopsy. The remaining seven cases have been taken from post-mortem records; their clinical and pathological reports have been scrutinized and all the available histological preparations re-examined. A case illustrating the erythroblastosis of neonatal syphilis is also included.

Among the terms which will be used in the ensuing pages are some which need preparatory definition. Icterus gravis neonatorum may be taken as a clinical term for a syndrome with certain constant and certain inconstant features, which will be described. Its most striking histological characteristic, and one shared with hydrops foetalis and, to a lesser extent, with anaemia haemolytica neonatorum, is the presence of widespread extra-medullary haematopoiesis. This feature, previously recognized in hydrops foetalis, and called by Rautman erythroblastosis foetalis, was first described in icterus gravis by the British workers Buchan and Comrie. More recently it has been found in anaemia haemolytica neonatorum as well. Erythroblastosis foetalis can only be established histologically, though its presence may be presumed in cases of foetal hydrops, icterus gravis, and the haemolytic anaemia of the newborn. By the term erythroblastemia is meant the appearance in the peripheral blood of nucleated erythrocytes definitely in excess of the physiological maximum for the age. Erythroblastemia occurs in every case of foetal hydrops and, at some stage, in nearly every one of icterus gravis.

The disease icterus gravis neonatorum, and its relationship to the syndromes of hydrops foetalis and anaemia gravis of the newborn, have

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recently been the subject of investigations by Diamond, Blackfan, and Baty (14) in America, and Parsons *et alii* (48) in England. Both groups of investigators have described cases illustrating the pathological resemblances of these conditions, which had already led to their being classed as varying clinical expressions of the same underlying condition, erythroblastosis foetalis.

Although hydrops foetalis has been recognized for some centuries, icterus gravis remained undifferentiated from other neonatal jaundices until late in the nineteenth. Anaemia gravis was first described by Ecklin (16) in 1919. Schridde (64) was the first to describe the extramedullary haematopoiesis in hydrops foetalis, whilst in the case of icterus gravis this was done by Buchan and Comrie (7).

Clinically, icterus gravis is usually a clearly defined disease; it is often familial, and there is a tendency for the first-born to escape. Subsequent infants may be stillborn or affected with icterus gravis, hydrops foetalis, or anaemia gravis, or a combination of conditions may be seen in the same infant. Thus oedema and jaundice may coexist or an icterus may fade to unmask a severe degree of anaemia. These clinical associations may be expressed diagrammatically (Table A).

TABLE A  
Erythroblastosis foetalis

Intra-uterine	Neonatal
(1) ↓ With universal oedema = hydrops foetalis *	(1) ↓ With severe jaundice and anaemia = icterus gravis neonatorum
(2) ↓ Without oedema *	(2) ↓ With severe anaemia and little or no jaundice = anaemia haemolytica neonatorum

\* Often stillborn.

Among the earliest English records of this disease is one by Ashby (3), who in 1884 reported a family of five children in which the last three died of jaundice soon after birth. Between this report and the pathological descriptions of the blood and organs of four cases by Buchan and Comrie in 1909, many examples of grave familial jaundice have been recorded, though a number of these are reported with insufficient detail for scientific study, and they appear under different classifications, rendering it clear that the views of the writers as to aetiology were many and varied. A review of the literature of erythroblastosis foetalis is given by Diamond, Blackfan, and Baty (14), and the present communication will only mention such cases as appear to illuminate its pathogenesis. Since the paper by Buchan and Comrie, attention has gradually focused on the relation of the erythroblastic process to the aetiology of the disease.

At a time when icterus gravis was emerging as a separate entity from simple icterus neonatorum, congenital biliary atresia, septic jaundice, and

syphilis with jaundice, the tendency was to regard its aetiology as in some way connected with a toxic or obstructive process. Thus Cruse (13) in 1880 regarded the probable cause as a shedding of biliary epithelium, Blomfield (5) in 1901 recorded, under the heading of congenital hepatic cirrhosis, a family in which the last three died of what was almost certainly icterus gravis, Lagrèze (35) in 1906 attributed it to toxic metabolites from the mother, Pfannensteil (52) in 1908 was unable to make up his mind, while Knoepfelmacher (33) in 1910 was of opinion that the syndrome is characteristic of septicaemia in the newborn. Pitfield (53) described cases in 1912 under the title of haemophilia neonatorum, M'gibbon (43) in 1912 regarded the erythrocytes as being abnormal, while Beneke (4), and Pfälzter (51) soon after, looked upon it as a bacterial intoxication possibly due to the *Bacillus coli*, which they recovered from various organs. Abt (2) in 1917 blamed the liver for failing in its extrahepatic functions, Wooley (72) in 1916 thought the disease to be in the nature of a new growth, and Rolleston (60) in 1920 considered it an hepatitis with ascending cholangitis due to maternal toxæmia. Subsequent investigations have been more and more in the direction of elucidating the abnormalities in the blood and blood-forming organs, but it is of interest to note that Buchan and Comrie themselves in 1909 reported closure of the bile-ducts and ampulla of Vater in their cases. In 1929 Hampson (23) suggested that in icterus gravis the newborn child fails to produce some antihæmolytic hormone previously provided by the mother. Articles by de Lange (37) 1932, Buhrman and Heyworth (9) 1931, and Ferguson (18) 1931, provide further evidence of the interconnexion of the erythroblastosis foetalis groups; de Lange favours maternal toxæmia as a cause, Clifford and Hertig (10) 1932, and Diamond, Blackfan, and Baty (14) 1932, both consider the syndrome a primary defect of the erythron, while the most recent paper by Parsons, Hawksley, and Gittins (48) 1933, regards the erythroblastosis as secondary to the hæmolysis and provoked by it.

While so much evidence has been obtained to show that icterus gravis neonatorum must be included under the class erythroblastosis, cases have been reported from time to time which by clinical, familial, and often hæmotological criteria were icterus gravis, but in showing certain clinical variations suggested that this syndrome may not be homogeneous after all. It is well known that icterus gravis may occur as a sporadic as well as a familial disease, and cases are on record in which it has not been accompanied by evidence of erythroblastosis in the blood (Hart (26), Greenwald and Messer (21), MacClure (42)). Maternal jaundice associated with the birth of infants with icterus gravis is mentioned in articles by Rolleston (59), Smith (65), and Nason (45). Nason's case was unique in that the mother's milk was coloured a deep yellow, a phenomenon once observed by us. The anaemia may persist, and gradually take on the qualities of a von Jaksch's anaemia as in the case of one of the infants in this article (Case 17) and also one quoted by Parsons; a family cited by Hichens (28) suggests a

possible relationship with acholuric jaundice, and Morris (44) published a case which remained jaundiced until its death at four and a half years.

The similarity between icterus gravis and the anaemia and jaundice associated with the excessive haemolysis of prematurity is stressed by Hampson (23), and will be discussed later in this article.

#### *Clinical Features*

In icterus gravis neonatorum previous children in the family may have been stillborn or affected with jaundice, anaemia, or universal oedema. Many isolated cases have, however, appeared in otherwise normal families. With few exceptions (Rolleston, 60) pregnancy has been normal, though hydramnios may occur, the infant is born at term, and the incidence of obstetrical difficulties bears no relation to the occurrence of the disease. The placenta may be normal or enlarged, the liquor amnii may be yellow, and the vernix caseosa golden in colour (65) (36). Abt (1) remarks that the coloration of the liquor amnii and vernix is to be explained by foetal excretion in utero of bile-containing urine, and such phenomena are therefore more to be expected in cases already jaundiced at birth (strong evidence that the processes responsible for the disease may be set in motion before the end of intra-uterine development). Many cases show little or no icterus at the time of birth, and in these the onset of the jaundice may be delayed for forty-eight hours or longer. Often the colour, first perceived in the face, spreads rapidly to the trunk and limbs; the conjunctivae are usually affected. With the development of jaundice other symptoms may appear, and drowsiness is perhaps the commonest of these. As a rule the faeces are well-coloured with bile-pigment which may be in excess. Exceptionally, they are pale or uncoloured for the first few days after the meconium has come away, and this may raise a strong suspicion of congenital obliteration of the bile-ducts, but in icterus gravis the stools never remain pale for long. In explanation of this temporary acholia three views may be quoted: first, that from excessive haemolysis the bile becomes too viscid to pass freely along the bile-channels (Still, 67), secondly, that damaged liver cells being taxed with excessive excretory work during a period of great haemolysis fail in their function, and thirdly, that accumulation of excess bilirubin in the bile capillaries, perhaps mixed with a foreign substance (MacClure, 42), leads to coagulation of bile-pigments (bile-casts or thrombi). Bile-pigments are found in the urine and sometimes bile-salts. Bilirubinuria diminishes with the lessening of jaundice and disappears before the urinary excretion of urobilin returns to normal. Albuminuria is exceptional and oliguria occurs only in the severest cases. In the results of van den Bergh's test there is no uniformity. Mild cases, and severe cases during recovery, may show a pure indirect reaction. Experience shows, however, that a biphasic reaction is the commonest

finding, though sometimes strongly positive direct readings are obtained, especially when the stools are pale, and our pathological investigations suggest the reason for this (see p. 168). Excessive haemolysis results in a varying degree of hyperchromic anaemia, and details of the blood changes will be described hereafter. The liver and spleen are always enlarged, particularly at the height of the haemolytic process. After recovery the spleen may be palpated for a time, but soon assumes a normal size. In cases which last a long time the organ becomes firmer as it diminishes in size.

If the anaemia is severe signs of dyspnoea will be apparent, recognizable in the young infant by exaggerated movements of the epigastrium which result from the resilience of the thorax and the increased excursions of the diaphragm. Signs have been found also in connexion with the circulatory system: there may be cardiac enlargement in which both dilatation and hypertrophy play a part, and murmurs are sometimes heard. Such symptoms occur in severe, and particularly in oedematous cases, and cyanosis may be present.

Sudden increases in the depth of the jaundice and exacerbations after apparent recovery has set in, occurred in several of the cases which we studied, a point not previously recorded. During these set-backs the drowsiness returns, the van den Bergh reading rises, and the anaemia increases. Spontaneous haemorrhage is an important symptom of the more severe cases and may feature in a relapse. Purpura is frequent and visceral haemorrhages are a pathological finding at autopsy. Umbilical and intracranial haemorrhage are recognized causes of death. The latter will be considered in connexion with the nervous manifestations of icterus gravis now to be described.

Convulsions, increased deep reflexes, and spasticity are not infrequent, though they are seen in only a minority of cases. Kernicterus (Schmorl, 63) or nuclear jaundice (Orth, 47) is a pathological conception, the symptomatology of which is too incomplete to permit as yet of anything more than occasional presumptive diagnosis. Judging by the figures of Schmorl (63), who saw six instances in 120 autopsies on cases of jaundice of the newborn, only about 5 per cent. of cases of icterus neonatorum may be expected to show nuclear staining. A survey of cases of kernicterus confirmed at autopsy (74) showed that death, if it occurred, is to be expected by the fifth day or earlier, though this rule is not without exception. The following symptoms have been reported in cases of kernicterus which have been established pathologically: drowsiness and apathy, convulsions and spasticity, and signs of medullary failure. We believe that paralysis of vital medullary centres is the usual mode of death (e.g. Case 2). A greater variety of neurological manifestations has been described in cases of kernicterus diagnosed clinically: choreo-athetoid movements, general muscular weakness and hypotonia, mental deficiency (Guthrie, 22); unconsciousness, mental deficiency, spastic diplegia, choreiform movements, muscular inco-ordination and rigidity (Spiller, 66); generalized muscular

rigidity and athetosis (Paul, 50); mental deficiency and epilepsy (Hoffmann and Hausmann, 29). While we are ready to accept such symptoms as sequelae of icterus gravis neonatorum, we do not consider it established that all of them are individually and invariably the result of nuclear jaundice. Spontaneous intracranial haemorrhage must always be considered as a cause for any organic nervous lesion, and, moreover, there is nothing to prevent an infant, already a candidate for mental deficiency or Little's disease, becoming affected with icterus gravis neonatorum.

Spontaneous intracranial haemorrhage occurred five times in our fifteen fatal cases, and was confidently diagnosed in a case which survived. It was more than twice as common as nuclear jaundice which was discovered twice among these fatal cases and was not suspected in any of those which survived. The nervous manifestations of the cases with spontaneous cerebral haemorrhage are not peculiar to icterus gravis and will not be enumerated. In Case 15 we were able to recognize the presence of haemorrhage by the sudden appearance of convulsions followed by separation of the cranial sutures and a bulging fontanelle; but for the latter sign kernicterus might well have been incorrectly diagnosed. In our opinion a diagnostic lumbar puncture should be avoided in such a case on account of the danger of causing severe haemorrhage at the site of tapping. A similar caution applies even more forcibly to puncture of the longitudinal sinus which is never justifiable in icterus gravis.

To complete the clinical picture it may be added that fever may be present, though it is not to be expected. The afflicted babies accept their feeds, though usually with diminished appetite, and they gain weight slowly. The risk of contracting enteral and respiratory infections in hospital is very great, and these infections probably rank with anaemia and haemorrhage as the chief causes of mortality.

#### *Differential Diagnosis*

*From icterus simplex neonatorum.* The occurrence of jaundice in the newborn brings first to mind the simple physiological icterus which occurs in some 33 per cent. or more of all births (60). This physiological variety, which is absent at birth, is mild and evanescent. An uncomplicated case shows no anaemia, oedema, haemorrhage, hepatomegaly, splenomegaly, or mortality. In cases of doubt the physician will be guided by the size of the liver and spleen, and by the blood picture. The physiological haemolysis of the newborn reduces the erythrocyte level from a characteristically high foetal figure, between 5.5 and 6.5 million per c.mm. down to 5-million cells, the process being accompanied by a fall in the haemoglobin, and a positive indirect van den Bergh reaction in the serum. This haemolysis, the mechanism of which is not understood, is believed to depend in part on the rise in oxygen tension which accompanies the change from placental to pulmonary respiration. It does not result in anaemia and the

infant's colour shows pink through a tinge of yellow. The pinkness of the skin may be tested by digitally expressing the blood from the capillaries and noting the resulting contrast in colour (23). In icterus gravis the haemolysis, beginning sooner, is more prolonged and severe, so that anaemia results, the infant becoming not only yellow but waxy pale as well. The presence of large numbers of nucleated red cells is important confirmatory evidence of icterus gravis neonatorum, but their absence does not necessarily exclude the diagnosis, because cases without erythroblastaemia have been recorded (21) (42) (74). Nevertheless, a nucleated red-cell count of more than 5,000 per c.mm. may confidently be expected in an early stage. The question may be asked: To what extent may normoblasts be found in healthy newborn infants? Experience shows (14) (20) that about 1,000 to 2,000 such cells per c.mm. may be encountered during the first few days in some 40 per cent. of cases, and that the total number diminishes day by day. Lippmann (41) refers to an exceptional case with 5,000 per c.mm., and our own observed maximum in icterus simplex was 4,928 nucleated red cells per c.mm. on the fifth day. For practical purposes we fix the physiological maximum in full-time infants at 5,000 per c.mm., and of these the majority are pyknotic normoblasts. In premature infants the figures may be somewhat higher. Soon after the onset of icterus gravis neonatorum 25,000 per c.mm. or more nucleated red cells are commonly seen, and they reach a peak some days after birth, to disappear from the circulation about the third week. Erythroblasts, and often megaloblasts, occur as well as the normoblasts. The chief difficulties in diagnosis arise in cases of icterus simplex complicated by certain neonatal diseases in which symptoms directly suggestive of icterus gravis may occur. In icterus simplex complicated by melaena neonatorum the liver and spleen are not enlarged, and in our experience, as in that of Clifford and Hertig (10), these cases of melaena do not show erythroblastaemia, though severe anaemia from haemorrhage may develop. With congenital heart disease as the complicating factor, dyspnoea and cyanosis may be added to the jaundice, together with oedema and even slight splenic enlargement, and if a cardiac murmur be absent diagnosis becomes extremely difficult. In congenital morbus cordis anaemia should not be present in the neonatal period, nor in our experience does erythroblastaemia occur. Icterus simplex with obstetrical intracranial haemorrhage may also mimic icterus gravis with or without kernicterus, but examination of the liver, spleen, and blood should prevent error.

*From excessive haemolysis of premature infants.* Haemolysis in premature infants sometimes results in early and prolonged icterus, in anaemia, and in some erythroblastaemia. Confusion with foetal erythroblastosis may be avoided by remembering that subjects of the latter disease, when prematurely born, are likely to show initial jaundice, universal oedema, haemorrhages, and early and severe anaemia. Premature infants with simple excessive haemolysis are less ill and show little or no splenomegaly (Case 16).

Nevertheless, the distinction is difficult and the conditions merge one into the other.

*From congenital obliteration of the bile-ducts.* In obliteration of the bile-ducts jaundice appears in the second or third week of life and steadily increases. The stools are pale from birth or turn pale later, but once pale they remain so. The blood picture of icterus gravis is not present. The clinical features of congenital bile-duct atresia show certain variations which make the diagnosis more difficult. Thus the stool may be coloured by bile excreted directly into the large intestine and a loose, uniformly yellow stool, or a firm clay stool, bile-stained on the outside, results. If a physiological icterus occurs on the third day and passes imperceptibly into the obstructive jaundice of bile-duct atresia, a stool so coloured may deceive the best clinician into a wrong diagnosis until a careful examination of the blood is made.

*From congenital syphilis.* Because the newborn syphilitic infant may show the symptoms of splenomegaly, hepatomegaly and jaundice, the investigation of every case of icterus gravis neonatorum should include a detailed family history and Wassermann tests on the infant and its parents, together with radiographic examination of the long bones. And the resemblances are even closer: anaemia, often of severe haemolytic type, may occur in the newly-born syphilitic infant and erythroblastæmia accompany it. Indeed, the clinical and pathological resemblances between foetal erythroblastosis and some cases of neonatal syphilis are so close as to suggest that the mechanism producing the anaemia, and the erythroblastic response to it, are common to both (illustrative Case 19). Here the analogy ceases: in icterus gravis neonatorum, and in the related conditions, the Wassermann reaction is always negative and the histology of syphilis is not encountered.

*From neonatal sepsis with jaundice,* usually the result of umbilical infection, the differential diagnosis is aided by remembering that jaundice from sepsis develops at a later date. The spleen does not enlarge unless systemic infection occurs, and then a swinging temperature may be accompanied by a positive blood culture. Fever does not exclude icterus gravis, and in the terminal stages of complicating infections positive blood cultures have been obtained in it as well.

*From catarrhal jaundice.* Most of the neonatal cases reported as catarrhal jaundice are probably either physiological icterus associated with mild enteral infections, or cases of icterus gravis which have recovered spontaneously. The conception of catarrhal jaundice (epidemic hepatitis) as a disease of the neonatal period is an improbable one, and its occurrence at this time is contrary to what we should expect of the comparative immunity of the newborn infant to most similar infections, and to its rarity in later infancy (40).

*From family acholuric jaundice.* Cases of acholuric jaundice have been recorded manifesting symptoms as early as the end of the second week

(Poynton, 54). In order to exclude this diagnosis the family history and a fragility test are required.

*From leukaemia.* A superficial examination of a blood film in any severe case of foetal erythroblastosis may lead to confusion with leukaemia, particularly if the normoblasts are mistaken for small lymphocytes and the megaloblasts either for lymphoblasts or for immature myeloid cells.

#### *Changes Observed in the Peripheral Blood*

As already mentioned, the blood picture of erythroblastosis foetalis is common to hydrops foetalis, icterus gravis neonatorum, and anaemia haemolytica neonatorum (or, as it is sometimes called, congenital anaemia). For convenience the different cell systems will be discussed separately.

*The erythron.* Our conception of the erythron in the foetus differs from that of the post-natal period, which again is not the same as in adult life. In an early period of intra-uterine development erythropoiesis is widespread in the tissues, but later it becomes a function particularly of the liver and spleen until towards the end of pregnancy, when the bone-marrow gradually appropriates it. At birth, according to the degree of this change-over from erythropoiesis in the viscera to erythropoiesis in the bone-marrow, so is the amount of extramedullary erythrocytogenesis to be measured. It is reasonable to argue that the change should be complete, or almost complete, at term, but a delay in the disappearance of extramedullary erythropoietic foci is a normal variation and certainly to be expected in prematurity. In erythroblastosis foetalis, as in prematurity, and perhaps in other disorders, this change is subject to considerable delay. The persistence of extramedullary erythropoietic foci well beyond term may with convenience be entitled erythroblastosis, and the presence of numbers of nucleated erythrocytes in the blood-stream, which nearly always accompanies it, may be alluded to as erythroblastaemia.

In icterus gravis neonatorum the changes in the erythron are indicative of two processes: severe destruction and compensatory regeneration. The former manifests itself by rapid decrease of erythrocytes, a positive indirect van den Bergh reaction which may reach thirty-five units or more, and the excretion of urobilinogen and urobilin in excess; the latter by the appearance in the circulation of immature erythrocytes in large numbers and a quick rise in the erythrocyte count as soon as the haemolytic process is checked. The number of immature red cells usually rises to a maximum after the improvement in the erythrocyte count has begun and then falls rapidly, the more immature cells disappearing first and the reticulocytes finally coming to rest at their normal level of under 1 per cent. shortly before recovery is complete. In a number of recovering cases the red cells do not rise above about 4,000,000 per c.mm. for a considerable time, and in these a raised reticulocyte count of about 3 to 5 per cent. suggests that

haemolysis, slightly above physiological limits, is persisting. The confused nomenclature of nucleated red cells makes their classification unsatisfactory: the term *erythroblast* is here used to denote all the intermediate stages when the cytoplasmic basophilia of the megaloblast is giving place to haemoglobin formation, while the term *normoblast* denotes the later stage when nuclear pyknosis has occurred. This nomenclature is used by Doan, Cunningham, and Sabin (15) (61) and has been noted recently in Schäfer's text-book of physiology (62). The exact demarcation between erythroblast and normoblast is of necessity arbitrary. Of the abnormal cells the megaloblast and erythroblast are the first to disappear, then the normoblast, and finally the number of reticulocytes returns to normal. Polychromasia occurs and parallels approximately the reticulocytosis. Punctate basophilia is usually seen: the stippled cells are not numerous and do not persist for long. Cases are recorded in which the erythrocyte count does not fall below four millions, and in these the outpouring of immature cells is proportionately less, but adequate serial counts on these cases are for the most part lacking. Although the anaemia varies from case to case it is usually severe, and counts lower than half a million are recorded. The changes in the erythron in icterus gravis closely parallel those seen in other haemolytic or erythronoclastic anaemias in infancy, as recorded by Parsons and Hawksley (49). Of special importance are its resemblances to the anaemia, often accompanied by jaundice, following the excessive haemolysis frequently seen in premature babies; and to the physiological icterus of the newborn. The excessive haemolysis of premature infants is non-familial, and usually benign, shows a moderate fall in erythrocytes, a compensatory reticulocytosis, and a positive indirect van den Berg reaction. The colour index is at unity, or more frequently above. Case 16 forms an example of this. The difference in the haematological pictures is only one of degree, and there is an apparent merging of the types, so that all may be regarded as reactions of the newborn infant's erythron to haemolysis, and the relation of the underlying causes in these conditions would appear to be close.

The individual characters of the erythrocytes in icterus gravis are important; besides the changes already described, anisocytosis becomes apparent and is more obvious at the height of the erythropoietic response. At this time all varieties of nucleated red cell are usually to be observed and the phenomena of karyokinesis, karyorrhexis, and nuclear extrusion are in evidence. The size of the red cells in this disease may be calculated by means of the haematocrit and by the Price-Jones curve. The difficulty of obtaining a sufficiency of blood from infants so ill has prevented adequate investigation of the cell volume in most cases, but a series of Price-Jones curves has revealed certain changes, which may be peculiar to foetal erythroblastosis and indicates the probable relationship of this form of haemolysis to that occurring in the premature infant. Although the method of Price-Jones has been extensively used by him in investigating normal and pathological blood (55), it has not yet been adequately applied to the blood

changes in infants. Van Creveld (12), in an investigation into the blood of normal babies and prematures during the first eight weeks of life, found that the mean erythrocyte diameter at birth was approximately  $8.0\ \mu$  (actually  $8.084\ \mu$  for premature, and  $7.99\ \mu$  for full-time babies) in comparison with a normal adult mean diameter of  $7.2\ \mu$ . In both, after a slight initial rise, there is a drop in the mean diameter over the first eight weeks, in other words, an approach to the adult size. This drop is, however, greater in premature than in full-term infants. Furthermore, he investigated one case of icterus gravis, and while the mean diameter was  $9.215\ \mu$  on the third day of life, it subsequently showed a fall even more rapid than is seen in premature infants. His cases all show greater anisocytosis than is present in the adult, but he does not give the variability or coefficient of variation, so that if his mean diameters and actual curves be used as standard, his variabilities cannot be so used. He is of opinion that the more rapid fall in mean diameter in the premature infants is related to the greater haemolysis known to occur in them, but in the case of icterus gravis he puts it down to exhaustion of the marrow, for which no reason is given.

Four full-time cases of the present series have been investigated by the Price-Jones method. As no one of these was seen during the first week of life, no confirmation of the early increase in mean diameter was obtained. In each case, however, when compared with the results of van Creveld

TABLE B

*Mean Diameter of 500 Erythrocytes*

Age in weeks.	Full-time infants (van Creveld).	Mean diameter of 500 R.B.C. ( $\mu$ )				
		Van Creveld's case of icterus gravis.	Icterus gravis. 1	Icterus gravis. 2	Icterus gravis. 3	Icterus gravis. 4
1	7.998	9.215	—	—	—	—
2	8.159	—	—	7.36	8.09	—
3	8.243	7.413	—	—	7.79	—
4	8.266	—	8.148	—	—	7.321
5	7.945	—	7.3	—	—	—
6	7.721	—	—	—	—	—
7	7.858	7.212	—	—	—	—
8	7.728	—	—	—	7.37	6.936

(Table B), a more rapid fall of mean diameter is found than occurs in the normal child or the premature. This confirms van Creveld's case. His explanation of the phenomenon on grounds of marrow exhaustion is not tenable on the evidence of our four cases, for the number of reticulocytes and immature cells showed that the erythropoietic tissues were hyperactive at the time when this phenomenon was occurring. It is much more probable that, in accordance with his explanation of the fall seen in the premature infant, a still greater diminution in mean diameter is occurring from the effects of a more severe haemolytic process. It is of interest that a similar reduction of

the mean diameter may be seen in a chronic haemolytic anaemia, such as acholuric family jaundice. This condition had been put down to a congenital defect of the marrow, in which the erythrocyte is of smaller diameter than normal, but of greater thickness, and unduly fragile in hypotonic saline. Evidence from haematocrit readings in one of our cases of icterus gravis showed that the average cell volume was not only above normal, but was still rising when the mean diameter was falling, a phenomenon indicating an increasing thickness of the cells. Further investigation may show that when a haemolytic process becomes chronic, the red cells become smaller and thicker in response.

The reaction of the erythrocytes to hypotonic saline is inconstant, some cases show a slight increase in fragility, others show no abnormality. In the former cases doubt may arise in diagnosing mild icterus gravis from acholuric family jaundice revealing itself in the neonatal period.

The progress of the recovery, as seen in the peripheral blood, is not infrequently interrupted by exacerbations of the haemolytic process; these produce a fall, often of a million cells or more per c.mm., occurring in a few hours; the van den Bergh readings show a rise and the child may appear clinically more ill at these times. Such set-backs are no doubt capable of causing death if severe enough, and they do not always evoke a further haemopoietic response, because this may be maximal at the time in question. The use of blood transfusion in treatment will be mentioned later, but it may here be said that the effect is seen most strikingly in the raising of the red-cell count and haemoglobin content of the blood. Study of our cases has shown that the haemolysis may effect the transfused blood, the count falling in a day or so by a greater number of cells than can be accounted for by the destruction only of the infant's blood. In other words, the haemolytic process, since it destroys also the normal cells of the donor, would appear to be a primary factor rather than an effect due to an abnormality of the infant's cells. An increase in the immature cells of the blood may be seen after transfusion.

Trought (69) has shown that in the first month of life the dissociation of haemoglobin into acid haematin, when hydrochloric acid is added, takes from thirty to sixty minutes as opposed to forty to sixty seconds in the adult. Consequently, we considered it inadvisable to use the Sahli method of haemoglobin estimation. On the other hand, it was found that carboxylation, and the use of the Haldane standard, resulted in an abnormal tint, the icterus gravis blood being of brick-red colour however long it was exposed to carbon monoxide; the normal colour is pink. One of us (J. C. H.) had previously noted this difficulty in matching, when working with the blood of certain premature babies. At first we thought that the tint was altered by the yellowness of the serum, but this is unlikely as a true match can be obtained with the indirect van den Bergh figure standing at 30 units. It is probable that there is some specific difference in the haemoglobin molecule, akin to the findings of Trought, which resists complete carboxyla-

tion.<sup>2</sup> Dr. W. W. Payne kindly investigated one case for us and found that it was impossible to produce more than 70 per cent. carbon monoxide saturation even some days after the disease had commenced.

*The thrombocytes.* Different observers have recorded cases in which the platelets were increased, decreased, and normal. The diverse methods of counting, the normal variation from method to method and from observer to observer, the lack of information on the thrombocytes in infancy, and the numerous factors that influence them, make it probable that variation through a wide range may normally occur. Our series have shown such variation, some certainly below normal numbers, and others normal, but none definitely raised. These findings agree with those of Parsons *et alii* (48). The discrepancy in the results of different observers may be due to different phases of the disease being studied. Diamond, Blackfan, and Baty (14) report a low thrombocyte count in the first few days, followed by a rise to normal. The haemorrhagic tendency, particularly at the height of the jaundice, may be recalled.

*The leucocytes.* In infancy the leucocytes form such a labile system that it is difficult to estimate the significance of all departures from the normal. The tendency to react to the disease and its complications should remind us that, whereas certain changes in the leucocytes are doubtless primary, others are probably dependent upon the course pursued in the individual patient, and secondary infections with their accompanying white-cell changes are very common. When seen at an early stage in the disease, there is a leucocytosis which varies in degree but is frequently above 35,000 per c.mm. As the disease is checked this figure falls, to rise again from any further stimulus—a bout of haemolysis or a complicating infection. The rise in the white-cell count is due chiefly to an increase in the granulocytes. Here again the swift changes in the normal infant's count over the first weeks of life, together with the variation encountered from case to case, must be remembered. The appearance of immature cells of the granulocyte series is the rule, principally metamyelocytes and unsegmented neutrophils, but at the height of the regenerative process myelocytes and myeloblasts are commonly seen in the blood, though they rarely form more than 5 per cent. of the total white cells. No immaturity of the lymphocytes was seen in the cases which we report. Diamond, Blackfan, and Baty (14) state that immature cells of every type are present, but this has not been found by others. At the onset of the disease there is no characteristic change in the eosinophile or basophile cells, but as recovery occurs the number of eosinophils very frequently rises both absolutely and relatively. This phenomenon has often been recorded and has been observed during recovery in most haemolytic anaemias. A similar, less constant, rise in the monocyte count occurs in some cases over the same period.

<sup>2</sup> In a recent paper J. Barcroft has discussed the physiological differences between the foetal and adult types of haemoglobin (*Lancet*, 1933, ii. 1021), and has given references to the work done concerning the foetal haemoglobin.

*Morbid Anatomy and Histology*

The main clinical and pathological features of foetal erythroblastosis, a term which includes hydrops foetalis, icterus gravis, and haemolytic anaemia of the newborn, are: 1. Haemolytic anaemia. 2. Large excess of nucleated red cells in the blood. 3. Extensive extramedullary haematopoiesis. 4. Icterus. 5. Enlargement of liver and spleen. A statement of the post-mortem findings in fifteen cases, fatal at different stages of icterus gravis, illustrates the parts enacted in each system, and by avoiding the description of a too static pathology we have aimed at an understanding of the central processes, as well as their concomitants in the various organs.

*Liver.* Until recovery is well advanced, enlargement of the liver is the rule. In the earlier stages there is vascular congestion and an increasing infiltration with bile. The gall-bladder and bile-ducts are always normal, though the bile may be thick and scanty.

From birth until the anaemia improves, or a fatal issue previously ensues, histological examination demonstrates capillary congestion and a widespread erythropoiesis. Groups of developing red cells are seen in the sinusoids, separating the columns of liver cells or seeming to replace them, and a more diffuse erythropoiesis may be observed in some of the capillaries. The earlier and the more severe the case the more immature are the developing blood cells, and often a striking resemblance to foetal histology is observed (Figs. 1 and 2). In addition to erythropoiesis, granulopoiesis occurs and, according to our observations, tends to centre in the portal tracts and vessels, where myelocytes are usually to be seen. Degenerative changes in the polygonal cells have been a conspicuous feature of our cases and have been mentioned by numerous other observers. These changes consist in diminished staining affinity, cystoplasmic vacuolations, and loss of cell-outline. Sections obtained from cases dying during the first few weeks (approximately three to eight weeks) show an erythropoiesis, diminishing as the age at death increases. Meanwhile, deposits of bile-pigment soon become one of the most conspicuous features. The pigment is deposited as fine granules in the polygonal cells, as coarser droplets in the bile capillaries, and as casts in the bile-ducts. Here and there a polygonal cell is seen with a large vacuole filled by a droplet of bile. As time goes on granules of iron pigment collect in the polygonal cells and in Küpffer's cells and a positive Prussian-blue reaction will be obtained. Some of the less-damaged polygonal cells begin to recover and others proceed to a stage of atrophy. In seven out of nine cases, which survived for five weeks or longer, we demonstrated the development of a fine fibrosis particularly among the polygonal cells of the atrophic areas and in the neighbourhood of the portal tracts (Figs. 3 and 4). With rare exception no infiltrating inflammatory cells were visible, though young proliferating fibroblasts were sometimes seen. The state of the liver after complete clinical recovery had taken place was studied in a case dying of pertussis at ten weeks (Case 14). Here it was

noted that the bile-pigment had disappeared, a few normoblasts and some haemosiderosis were still present, and no fibrosis had taken place. Cases with incomplete recovery had a survival period between five weeks (Cases 10 and 13) and ten months (Case 17). Fibrosis when present tended to assume a distribution mainly lobular and was seldom pronounced. Pseudo-bile canaliculi were not recognized, and the bile-ducts were always healthy.

*Spleen.* The spleen, like the liver, is enlarged at all stages and congestion of the pulp is the rule. In the neonatal period the Malpighian bodies are normally not apparent to the naked eye and are minute in microscopical preparations. This is also found to be the case in icterus gravis. The accumulation of bilirubin, and later of haemosiderin, follows the same course as in the case of the liver, though bile-staining is less. The earlier stages of the disease are marked by widespread erythropoiesis and granulopoiesis, which with recovery diminishes. Degenerative changes have not been reported, nor did we find them, though we noted evidence of fibrosis in four cases (Cases 6, 10 (Fig. 9), 12, and 14), and in three of these the reticulum showed increased density and staining affinity.

*Kidney.* Comparatively few studies in the morbid anatomy of the kidney in icterus gravis have been made. We have found a lesser degree of erythropoiesis than in other solid viscera. The chief histological changes are the result of an attempt to excrete the products of excessive haemolysis. The epithelial cells, particularly of the convoluted tubules, show granules of bile-pigment and haemosiderin. Naked-eye examination of fresh specimens shows icterus, chiefly of the cortex, and large amounts of uric acid deposited in the collecting tubules, apparent as yellow linear striations converging towards the apex of each pyramid. Microscopically the tubules are often dilated behind these accumulations (38) and occasionally local necrosis takes place in their vicinity, irregular cystic spaces resulting (Case 13). It is held that the uric acid which is excreted in such quantity is derived from the nuclei of normoblasts after extrusion. Similar deposits may be seen in normal newborn infants during the first ten days, and in cases of severe haemolysis and anaemia at other ages. The glomeruli are usually normal, but their capsules may be slightly dilated. Interstitial haemorrhages may be seen.

*Other tissues.* Extramedullary haematopoiesis has been described in the pancreas, adrenals, gonads, intestinal tract, lymphatic glands, placenta, connective tissues, skin, and in other situations [Buchan and Comrie, 1909 (7), Rehn, 1912 (57), Ylppö, 1918 (73), Diamond, Blackfan, and Baty, 1932 (14), Lightwood and Hawksley, 1933 (38), and numerous other workers].

*Bone-marrow.* Investigators have agreed in finding the bone-marrow hyperplastic for all elements, though Diamond, Blackfan, and Baty reported occasional reduction in the number of megakaryocytes. We have seen evidence of brisk haematopoiesis in all the marrows we have examined. As regards erythropoiesis, there is a relative increase of the less-matured cells and a scarcity of fully developed erythrocytes. We have provisionally

concluded from these marrow studies that there is a shift to the left in the cell-pattern. We observed an increase of megakaryocytes, after recovery from icterus and anaemia, in the bone-marrow from a case (Case 14), in which thrombocytes had been diminished at the height of the disease.

*Heart.* Enlargement of the heart occurs in a few cases of icterus gravis, though it is more characteristic of hydrops foetalis (Schridde). The enlargement is partly from dilatation and partly from hypertrophy. In Case 10 there was concentric hypertrophy of the left ventricle.

*Nervous system.* The changes in the nervous system so far recognized may be divided into spontaneous haemorrhage and icteric staining. Intracranial haemorrhage was found in five cases in our series and was diagnosed in one surviving case. Usually these haemorrhages are subdural and cortical. In our most severe example haemorrhage largely filled the subarachnoid space, extending also along the spinal cord (Case 8). Petechial haemorrhages may also occur.

Icteric staining is sometimes seen in the meninges, ependyma, and choroid plexus. Staining of the brain substance is rare in icterus gravis, and is said not to occur in other varieties of jaundice [e.g. congenital obliteration of the bile-ducts (74)]. The incidence does not depend on the intensity of the general icterus, and a toxic factor may play a part (Schmorl, Pfältzer, Hart, Hoffmann and Hausmann). The pathological anatomy and histology of kernicterus is detailed by Orth, Schmorl, Beneke, Ylppö, Zimmerman and Yannet, and others. Usually there is diffuse bile-staining of the glial tissue round injured ganglion cells. Our own personal experience of it, in Cases 2 and 3 (Figs. 5, 6, 7, 8, 10-15), is described in the protocols, and we are indebted to Drs. J. G. Greenfield and Denny Brown for valuable help.

*Muscles.* Zenker's degeneration of skeletal muscle has been described in a few cases (4, 51).

### *Aetiology*

In seeking for a satisfactory explanation of the cause of erythroblastosis foetalis in its various forms, the point on which the greatest difference of opinion exists is whether the erythroblastic process is provoked by the haemolysis, or whether it is a manifestation of a primary disease of the erythron to which the haemolysis is secondary. If the erythroblastosis is a primary fault, then the most adequate explanation of the haemolysis is that the cells liberated from the erythroblastic foci into the circulation are abnormally prone to destruction. If the haemolysis comes first the sudden demand for fresh cells at a time when the supply from the bone-marrow may be inadequate, and when extramedullary foetal blood formation has barely ceased, is held capable of reactivating this foetal mechanism, and the nature of the stimulus is believed to be such as to cause the outpouring of nucleated red cells into the circulation.

Recent writers on erythroblastosis foetalis have given support to both

these views; Diamond, Blackfan, and Baty (14) hold that the disease is a primary abnormality of the metabolism of the haematopoietic system, resulting in an outpouring into the blood of young and unstable cells, which undergo rapid haemolysis. Parsons *et alii* (48) believe in the hypothesis of a primary haemolysis. Our findings are in favour of the latter view, but it is obvious that neither theory will cover all the known facts. Hydrops foetalis may occur with erythroblastæmia before there is much evidence of haemolysis; and it may occur without erythroblastæmia (de Lange). Icterus gravis also may occur without erythroblastæmia. Finally, in icterus gravis a considerable erythroblastæmia may occur when the red cells have not dropped below 4 millions; though in the excessive haemolysis of prematurity the red cells may drop to 3 millions or lower without erythroblastæmia.

Even if we were able to decide this issue we have still to solve the problem of the underlying cause—either of the haemolysis or the erythroblastosis. In reviewing the literature of icterus gravis we have indicated the diversity of the opinions already advanced. Of recent years the advocates of bacterial infection as the cause have diminished, and we ourselves do not believe the evidence points that way. The possibility that toxins lie at the root of the disorder cannot lightly be dismissed. The association of haemolysis, liver-cell damage, and nerve-cell necrosis in many of the cases is difficult to explain on any other basis. The toxin or toxins might be (1) exogenous, in which case their origin and nature are almost entirely unknown; (2) endogenous. If the latter we might suspect that the products of haemolysis can exert a toxic action, and this has been suggested by Hampson (23). Bilirubin and bile-salts have each been blamed for the nerve-cell necroses of kernicterus. Because of its frequent familial occurrence Rolleston suspected icterus gravis of being an hereditary disease. Evidence in favour of this has never been properly sought ~~therefore~~, and the lack of it does not exclude the possibility of a Mendelian recessive. In one of our cases (Case 18) the parents were first cousins and familial icterus gravis had occurred among uncles and aunts, a fact suggestive of the action of a Mendelian recessive character. Associated congenital developmental defects occurred in three out of fifteen autopsies.

#### *Treatment*

Since the recognition of icterus gravis forty years ago singularly little has been written concerning its treatment. The most careful studies have been contributed by pathologists and, with certain important exceptions, the clinical papers have been of a descriptive nature. In 1910, Rolleston (59) recommended an attempt at ante-natal prevention by giving intestinal or biliary antiseptics to the mother in familial cases. In 1924, Fordyce and McAfee (19), on the recommendation of Robert Hutchison, gave similar treatment and a healthy child was born to the mother though previous

children had developed icterus gravis. In 1924, Klemperer (32) reported results obtained by intravenous infusions of glucose.

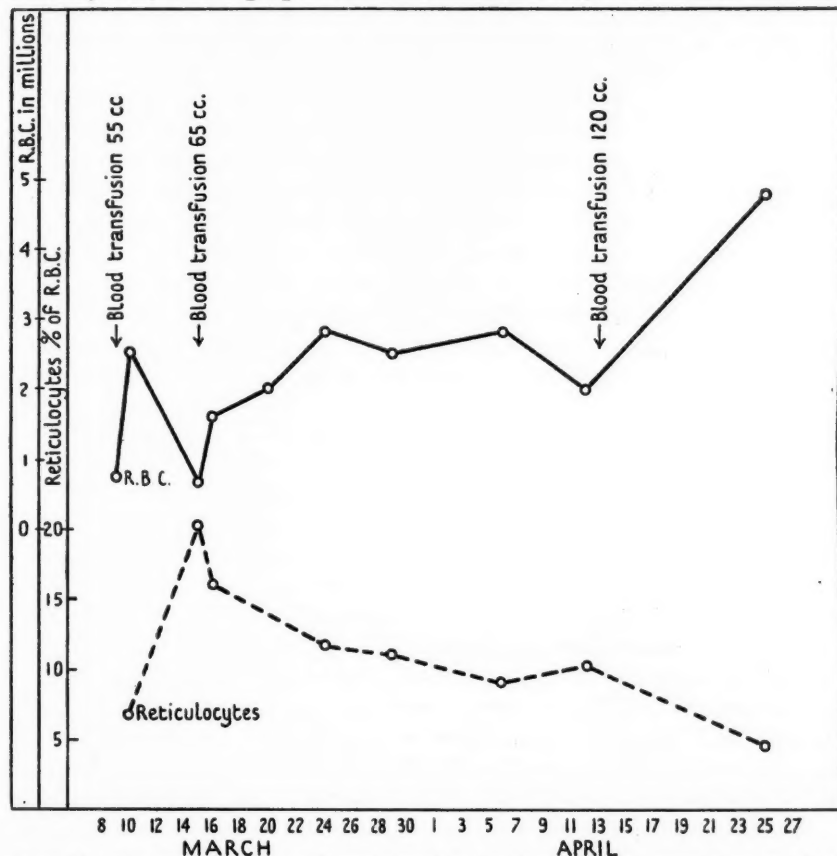
Regarding haemotherapy in its various forms, the principles were well-understood and enunciated by Opitz (46) in 1922. In the treatment of infantile anaemias he distinguished between the stimulation therapy of intramuscular blood injections and the substitution therapy of intravenous transfusions. In anaemias showing 'embryonic blood pictures' he held that stimulation therapy was contra-indicated because the marrow was already fully stimulated, and he argued against injections and in favour of transfusions. In 1925, Hart (26) was successful with an exanguination transfusion in one case of icterus gravis. Even prior to 1929 Arntzenius was a protagonist of whole-blood transfusion for icterus gravis, though de Lange was opposed to them during the first few days of the disease, but in that year she and Arntzenius (36) published a case successfully so treated from the onset. In 1930, Kleinschmidt (31) obtained cures with blood transfusions (75 c.c.) especially in cases showing erythroblastemia, while Buhrman and Sanford (9) failed to cure two similar cases with intraperitoneal injections of citrated whole blood. In 1931, Kramaztyk (34) used 'timely transfusions' and whole blood injections. Subsequently, Clifford and Hertig (10) recommended repeated transfusions for foetal erythroblastosis. As a donor they used either parent and did not find it necessary to type or cross-agglutinate; fluid was forced by mouth and saline infusions advocated. Diamond, Blackfan, and Baty (14) treated some of their cases of icterus gravis by blood transfusions and applied the same treatment in eight cases of haemolytic anaemia of the newborn. In 1933, we introduced into England the method of repeated blood transfusions by which we have obtained good results.

Treatment with human blood-serum was thought of in 1912 on account of mistaken diagnosis and confusion of terms in the mind of Pitfield (53), who described under the name of haemophilia neonatorum a family of infants fatally afflicted with icterus gravis. The last infant of this family he treated by injecting the nurse's blood-serum and blood in doses of 4 to 15 c.c. (72 c.c. in forty-eight hours) and recovery followed (method of injection not stated). This he did because Welsh (70) had successfully used human blood-serum injections for the haemorrhagic disease of the newborn (melaena neonatorum) called haemophilia neonatorum by Welsh. Pitfield evidently believed he was dealing with the same disease. In England, little interest was taken in either form of haemotherapy until 1929, when Hampson (23) published an account of the use of human blood-serum intramuscularly injected in eighteen familial cases of icterus gravis of which seventeen recovered. By this treatment he held that some antihaemolytic agent absent from the infant's blood and present in the adult serum, was supplied. He advocated the early administration of 5 to 15 c.c. of serum on successive days until bilirubin began to disappear from the blood. In 1933, the same author (24) modified his view, subdividing the cases and recommending injection of human blood-serum only in those without erythro-

blastaemia, but even in this group he admitted no objection to a transfusion of whole blood if the case be seen late in the disease.

The use of liver preparations has been proposed (11, 10, 24) and Cooley has suggested splenectomy (11).

At the Hospital for Sick Children we have confirmed that spontaneous recovery occurs in a proportion of the milder cases, a fact which must be



Case 14. The effect on the erythrocyte level and reticulocytes of repeated whole-blood transfusions.

recognized in assessing therapeutic measures. In our hands intramuscular injections of whole blood have not proved of benefit in cases with erythroblastaemia, and we have tried human blood-serum injections without success. On the other hand repeated transfusions of citrated whole blood have produced satisfactory results, even in some of the most severe cases. As our indication for transfusions we watch the erythrocyte level. Any case with substantially less than 4 million erythrocytes per c.mm. is transfused at intervals of four to seven days until the count is maintained spontaneously at or above that level. (See Graph, above.) Our transfusions have varied

from 40 to 120 c.c. in volume and from one to four in number. As many as six transfusions have been used in a single case by Diamond, Blackfan, and Baty. The volume of the transfusate may be calculated from the rule: 10 to 15 c.c. of blood per lb. of body-weight. Either parent may be the donor and we have relied on a direct matching of the donor's cells against the recipient's serum. In practice we have found that rapid haemolysis may continue even after transfusions have been given, evidence that the transfused blood acts by substitution and not by supplying any hypothetical antihaemolytic substance.

We advise the continuance of breast-feeding whenever possible, and the administration by mouth of glucose solution to protect the liver from damage. Infusions of glucose and saline are also to be recommended. This exhibition of fluid has a twofold object: to overcome dehydration should it be present, and to facilitate the excretion of the products of excessive haemolysis. So ready are these patients to contract the enteral and respiratory infections common in hospitals that we favour their treatment at home (39, 27) and we have found that a few hours in hospital are sufficient to perform the investigations necessary to the diagnosis and to administer a blood transfusion. Subsequent transfusions may be done from the out-patient department.

### *Prognosis*

Icterus gravis is a dangerous disease, and its mortality rate lies between that of hydrops foetalis and of anaemia haemolytica; the former of these is always fatal, the latter rarely so. The immediate prognosis is better than the ultimate, some cases which apparently recover subsequently develop mental deficiency, spastic diplegia, and possibly other disorders. Death, where it occurs during the progress of jaundice, may be from anaemia, haemorrhage, toxæmia, convulsions, or medullary failure; whilst death from intercurrent infection is common at a later stage. Very few authors have published statistics. Hampson (23), on analysis of Rolleston's and his own untreated cases, found an 80 per cent. mortality rate. Rapidly developing jaundice and severe anaemia are bad signs, and the chances of recovery are much enhanced by timely and adequate blood transfusion where it is required. Haemorrhages from the umbilicus or from the mucosae are of very grave significance and often result in death; medullary failure is most to be feared within the first five days. A single convulsion is of small immediate significance; repeated convulsions are serious and, if not in themselves fatal, are often indicative of intracranial haemorrhage or kernicterus, perhaps with subsequent mental change and spastic conditions of the limbs. The appearance of nervous manifestations makes the prognosis worse. Arrest of haemolysis, indicated by a steadying of the red-cell count and diminution of bilirubinaemia, followed by an improvement in the blood

picture, is a good omen, but further bouts of haemolysis may subsequently occur.

### *Sequelae*

No sequelae affecting the liver have been universally recognized. Morris (44) reported the case of a child jaundiced from birth and surviving in this state for  $4\frac{1}{2}$  years. Reports such as this suggest that an infant may sometimes survive the period of severe neonatal jaundice with a liver so damaged that recovery is either delayed or prevented. Cases mentioned by Still (67) point in the same direction. Proof that hepatic fibrosis may occur is supplied by our studies of cases 4, 6, 9, 10, 11, 12, and 13, and we suggest that the process of recovery is occasionally accompanied by cirrhotic changes. If this view be correct, and if survival into late infancy and childhood occurs, then there must of necessity be a group of hepatic cases which takes its origin in icterus gravis neonatorum. Idiopathic infantile (or juvenile) cirrhosis is the clinical condition to which our minds turned. This disease, like icterus gravis, may or may not be familial. It appears at various ages of infancy and childhood, usually earlier than late. It progresses to a fatal termination more speedily than Laënnec's cirrhosis in the adult and, like it, proves at autopsy to be a portal fibrosis, though occasionally a more lobular type is encountered. Except for the cases which develop out of congenital biliary obstruction, its aetiology is unknown and the evidence for any attempt to relate it with severe neonatal jaundice is absent by past neglect to obtain it.

No disease of the spleen has been ascribed to preceding icterus gravis, and the variety of splenic and splenomedullary diseases of unknown aetiology suggested that a study of this problem might be fruitful. Evidence has already been adduced that some cases of the sub-chronic haemolytic anaemia, known as the infantile splenic anaemia (or pseudo-leukaemia) of von Jaksch, may arise by a prolongation of the haemolytic process of foetal erythroblastosis (Case 17), and a case of chronic haemolytic jaundice with splenomegaly in a child reported by Sutherland (68) suggests a similar possibility. Further, our pathological studies of icterus gravis demonstrate that fibrosis may result in the spleen as in the liver, though less often. Little definite is known of the pathogenesis of splenic anaemia in children, a syndrome in which gross splenomegaly usually precedes hepatic cirrhosis (metasplenomegalic hepatic cirrhosis). Certain writers, Eppinger (17) and Hanau (25) among them, favour the proposal to regard splenic anaemia and Banti's disease as varieties of 'hepato-splenic cirrhosis', a group in which atrophic hepatic cirrhosis without splenomegaly forms one end of a series with splenic anaemia at the other. If, as seems probable, the underlying change is inflammatory as well as progressive in this disease, then icterus gravis neonatorum could stand only in relation to some, perhaps, of the infantile and juvenile cases by damaging either the liver or spleen, or both, and predisposing to subsequent inflammatory cirrhosis.

That permanent sequelae in the nervous system may result from kernicterus has been acknowledged since the work of Guthrie and Spiller, and the present paper provides new evidence that icterus gravis is one of the causes of subdural haemorrhage. Mental deficiency is the most important of the nervous sequelae of icterus gravis.

Naish supplies the following illustration: Male, deep icterus from second day, lasting six weeks. Pallor noticeable as jaundice faded, and obvious for some months. At seven months it was clear that he was mentally defective. No spasticity.

Unless the mental deficiency be associated with symptoms pointing to involvement of the basal nuclei, its dependence on the icterus is no more than an assumption of probability, and the same is true of diplegia and spasticity. Congenital athetosis and choreo-athetotic movements are perhaps the characteristic results of kernicterus; muscular inco-ordination, generalized rigidity and epileptic fits are suggested products.

*Hepato-lenticular degeneration. Progressive lenticular degeneration. Wilson's disease.* Wilson himself in the first description of progressive lenticular degeneration (71) saw a possible connexion between the anatomico-pathological distribution of the lesions he described and the kernicterus of Schmorl. His attitude may be summarized by the following quotation:

The analogy kernicterus offers to progressive lenticular degeneration is therefore highly suggestive. I do not wish to over-estimate the value of the analogy, however, and in drawing attention to it, and to the possibility of its opening up a new field of research, enough has been said at present.

Wilson believed that the syndrome he described was due to an unknown but highly selective toxin. No subsequent work has brought further light to Wilson's suggestion, and Zimmerman and Yannet (74) in a recent paper conclude:

'... it would seem that there are more differences than similarities between kernicterus and Wilson's disease and ... the two conditions are not causally related.

If our conclusion that hepatic cirrhosis be an occasional result of icterus gravis is correct, then a possible link is established between the two, though the long delay before the clinical appearance of the symptoms of hepato-lenticular degeneration would be a further problem.

*Bones.* Braid (6) has recorded a unique case in which icterus gravis was followed two years later by cystic changes in the bones. No further examples of this sequel have been recorded. The disturbances of calcium metabolism produced by jaundice have been recognized by several investigators [Ivy (30)] and osteoporosis has been noted in biliary fistula. The effects of ligation of the common bile-duct in growing animals was investigated by Buchbinder

and Kern (8) who divided between ligatures the common bile-duct in puppies and made biochemical investigations and radiological studies of the bones. They found a progressive fall in the blood-serum calcium to about half the normal values, but growth continued, and after one or two months, osteoporosis appeared. One puppy developed bilateral cysts in the bones. The same authors found reduced serum calcium levels in human obstructive, catarrhal, and haemolytic jaundice (only three cases). Some recent biochemical investigations by Roberts (58) suggest that the retention and/or formation of blood phosphatase is related to the functional activity of the liver, and he cites evidence that in obstructive jaundice the retention of phosphatase in the blood increases. We know of no other evidence that might conceivably link icterus gravis neonatorum with the unusual bone dystrophy seen in Braid's case. We have X-rayed the bones in some of our cases during the period of jaundice, and have noted no changes.

#### *Summary*

The time is passed when icterus gravis neonatorum can be regarded as an isolated disease. Evidence has accumulated which brings it into relation with hydrops foetalis on the one hand and haemolytic anaemia of the newborn on the other. Nor can the diagnosis be reserved for the familial cases which form only a proportion of the total. Its conception as a disease of the liver must also be widened and one of the objects of this communication is to study the parts played in the blood and blood-forming tissues. The blood changes consist in a rapidly developing anaemia, almost unanimously agreed to be haemolytic. There is a brisk response by the haematopoietic tissues which are intensely stimulated, and, with the outpouring of nucleated red cells, an embryonic blood-picture occurs.

The pathological findings consist in persistence of extra-medullary haematopoiesis and the cell-pattern of the bone-marrow shows immaturity and signs of regenerative activity. Cell degenerations and necroses occur in both liver and brain in certain cases. Among the known sequelae in non-fatal cases are anaemia and nervous manifestations. Evidence is given in this paper suggesting that some cases of idiopathic juvenile cirrhosis and splenic anaemia may take their origin in icterus gravis and that the aetiological background of hepato-lenticular degeneration may be related to kernicterus. The treatment of icterus gravis is discussed and the value of repeated blood transfusion is emphasized.

The cause of erythroblastosis foetalis, including icterus gravis, remains unknown, but we have concluded that there is more evidence for a primary haemolytic process than for a primary disturbance of blood formation. There is insufficient evidence definitely to incriminate a toxin (or toxins) though this explanation is suggested by certain of the facts. The possibility of an hereditarily transmitted factor has never been adequately investigated.

*Case 1. P. M. I. G. 2. 1933.*

*Female.* A familial case of icterus gravis neonatorum with oedema. Treated immediately after birth by intramuscular injection of human blood serum. Died at thirty-six hours old.

*Family history.* The family history was negative, except in the case of the preceding child who died of icterus on the fourth day of life. Two previous pregnancies had been normal.

*Clinical History.* After a normal pregnancy this infant was born at home, deeply jaundiced and slightly oedematous. The liquor amnii was stained yellow, the placenta was normal, and the vernix caseosa, though excessive in amount, was normal in colour.

10 c.c. of the mother's blood-serum were given into the infant's buttock a few minutes after birth. Subsequently the jaundice deepened and death took place at thirty-six hours. There was no blood count or other clinical investigation.

*Autopsy.* A restricted autopsy was permitted and carried out twelve hours after death. The following notes were made: Sclerema neonatorum of patchy, subcutaneous type, affecting particularly the face, thighs, and arms. Feet oedematous. Dark yellow ascitic fluid in peritoneum. Heart and brain not examined. Liver enlarged and engorged. Spleen enlarged and engorged. In a rib and a femur the bone-marrow was red throughout the medullary cavity.

*Histology.* The histology of the liver, spleen, and skin was studied by us in paraffin sections stained with haematoxylin and eosin, by van Gieson's stain and the ferro-prussiate method for iron. The erythropoiesis was studied in sections fixed by Helly-Maximow's method and stained with Leishman's stain.

*Liver.* The polygonal cells showed vacuolation and other degenerative changes. The cytoplasm and nuclei took the stains badly; in many areas there was either cytolysis or shrinkage. There was an extensive deposit of fine, intracellular bile-pigment. Erythropoiesis was widely distributed, both irregularly in the capillaries, and also in an orderly manner arranged in well-defined nests apparently within the liver sinusoids (Fig. 18). The erythropoiesis was predominantly normoblastic, but numerous megaloblasts and erythroblasts were also to be seen. There was no haemosiderosis and no fibrosis. Granulopoiesis, though present, was not a feature: the myelocytes were seen particularly in relation to the portal tracts and vessels.

*Spleen.* The capsule and supporting tissue were normal and there was no fibrosis. The reticulum was normal and the splenic pulp anaemic. The Malpighian bodies were so small that they were with difficulty found. Erythropoiesis was much in evidence, and its stage was predominantly normoblastic. Granulopoiesis was inconspicuous. There was no haemosiderosis and very little bile-pigment.

*Skin.* No histological abnormality was noted in the portion of skin which we examined, except that the areolar connective tissue immediately beneath the cutis vera was, in many places, actively erythropoietic and granulopoietic, and bore a striking resemblance to a section of bone-marrow. No bile-pigment was seen, and no histological evidence of sclerema neonatorum.

*Case 2. P. M. 404/33, 1933.*

*Female.* A case of icterus gravis neonatorum. Kernicterus. Death on fifth day.

*Family history.* The parents were healthy and there had been no miscarriages. There was no family history of any variety of jaundice, except one male child aged 11 months who was born at full term and had been slightly jaundiced.

*Clinical history.* Pregnancy was normal, but abortifacients were used and there was an attempted instrumental abortion. The baby was born at term, slightly jaundiced. Labour had been normal. The liquor was not excessive and not yellow. The vernix was increased, but not yellow. The placenta appeared to be normal. On the fourth day the jaundice suddenly deepened, vomiting occurred with slight haematemesis and melaena, and signs suggesting some cerebral lesion developed. 15 c.c. of whole blood were given intramuscularly on this day and she was admitted to hospital.

*Examination.* Deeply jaundiced, but not obviously anaemic. Respiration rate very slow (about 1 per minute), pulse imperceptible. She died early on the fifth day of life, 1½ hours after admission.

*Autopsy.* Seven hours after death. Skin jaundiced to a dark lemon tint. Brain: kernicterus. Heart icteric, not enlarged. Liver slightly enlarged, not much bile-stained, bile-ducts patent. Gall-bladder normal and containing green bile. Spleen enlarged and congested. Intestines contained yellowish-green, faecal material. Kidneys slightly icteric with orange striations of pyramids. Bone-marrow dark red throughout ribs, femora, and tibiae. During life there was no opportunity of examining the blood. A post-mortem blood smear stained with Leishman's stain showed, in addition to erythrocytes, the presence of large numbers of white cells, the type of which could not be determined on account of post-mortem changes, but many immature forms were seen; numerous erythroblasts and normoblasts were also present.

*Histology.* The histology of the liver, spleen, and kidney was studied in sections stained with haematoxylin and eosin and in sections fixed by Helly-Maximow's method and stained with Leishman's stain.

*Liver.* Liver-cell columns rather widely separated but capillaries only slightly engorged. Nuclei of polygonal cells stained badly; their cytoplasm contained golden-yellow granules of bile-pigment. There was evidence of some cytoplasmic degeneration and disappearance of cell-outline but no vacuolation. Nests of normoblasts were seen and also islets of granulopoiesis, not confined to the portal tracts. Subcapsular haemorrhage.

*Spleen.* Malpighian bodies of normal size and number. More evidence of granulopoiesis than of erythropoiesis. Deposition of bile pigment.

*Kidney.* Subcapsular and interstitial haemorrhage. A few nucleated red cells in capillaries. No other abnormalities.

*Bone-marrow.* The preservation of the tissue was unsuitable for cytological studies.

*Morbid anatomy of brain.* An horizontal section, cut below the centre of the optic thalami and through the internal capsules (Fig. 7) showed that there was an almost symmetrical icteric staining of the grey matter of the basal ganglia. In addition, the columns of the fornix, the grey matter of

the hippocampus (cornu ammonis) (gyrus dentatus), certain portions of the cerebral cortex in the frontal and occipital regions and in the island of Reil, were affected. Almost everywhere the staining was limited to the grey matter. Thus in the hippocampal region neither the fimbria hippocampi nor the alveus were stained. Except for the cornu ammonis, the affected portions of the cerebral cortex were much less densely stained than the nuclear masses.

Entering into somewhat more detail with regard to the corpora striata and the optic thalami, it was found that the staining was present throughout the caudate nucleus, and involved both the putamen and the globus pallidus of the lenticular nucleus, being denser in the putamen than in the globus. The claustrum was not identified. It must be remembered that the undifferentiated state of the neonatal brain makes difficult the identification of certain of the nuclear masses. In the optic thalami the anterior and medial nuclei were stained, but only part of the lateral nuclei, the region of the pulvinar escaping. It may be noted that the lateral nucleus of the thalamus is extensively pervaded by white fibres, a possible explanation of its escape. As far as could be judged, the central nucleus of Luys and the nucleus arcuatus were also stained.

In the region of the corpus pineale staining of the nucleus habenulae was noted. The pineal body itself was probably stained but was not identified with certainty.

At the base of the brain an external examination showed that the flocculus of the cerebellum was bilaterally and symmetrically stained and the corpora mamillaria were also picked out.

A vertical section through the centre of the brain showed intense icterus of the nuclei in the floor of the fourth ventricle, and dissection showed a similar colouration of the grey matter in the tegmentum (nucleus ruber). The dorsal grey matter of the midbrain was faintly stained in the region of the oculomotor nuclei. There was a slight staining of the basilar portion of the pons.

The grey matter of the cerebellar cortex and the dentate nucleus was diffusely stained, and this staining included the lingula but not the anterior medullary velum. The white matter of the arbor vitae escaped entirely. As regards the medulla and spinal cord, it was unfortunate that only a small portion was still attached to the brain when it came to be examined. The grey matter of the inferior olivary body on each side was very intensely stained (Fig. 8).

After prolonged immersion in formalin solution the staining pigment remained yellow and gradually faded. Bile-pigment in tissues exposed to formalin, when due to obstructive jaundice, turns green and does not fade.

*Histology of the brain.* Celloidin sections were stained by Nissl's method, by haematoxylin and eosin, by van Gieson's stain, and frozen sections for fat. In staining for the yellow pigment care must be exercised to avoid washing it away with xylol. Histologically this yellow pigment, which appears to be a modified bilirubin, was distributed in two ways: intracellular and extracellular. In the former case it appeared as a diffuse yellow-staining of the cytoplasm; in the latter as a diffuse staining of the intercellular ground-substance.

*Inferior olivary body.* Here the pigment was seen in the ground-substance, following accurately the wavy band of ganglion cells which makes up this nucleus (Fig. 8). The ganglion cells appeared normal.

*Nuclei in the floor of the fourth ventricle.* Here there was staining of the ground-substance and also of the cytoplasm of some of the neuroglial and ganglion cells, and nerve-cell degeneration was evidenced here and there by shrinkage, distortion, and an excentric position of the nucleus. There was little infiltration or sign of phagocytosis.

*Basil ganglia: Thalamus.* Here pigmentation of the ground-substance was seen and some lymphocytic cuffing of the perivascular spaces. The ganglion cells appeared normal. Globus pallidus: changes essentially similar to those described above for the nuclear grey matter in the floor of the fourth ventricle, that is to say, bile-staining and degeneration of certain of the ganglion/neuroglial cells.

### Case 3. W. P.

*Female.* A fatal case of icterus gravis neonatorum. Kernicterus.

*Family history.* The father had been jaundiced two or three weeks before the birth of this infant; this illness was regarded as an attack of 'catarrhal' jaundice. The patient was a sixth child: four were alive and well; the other was prematurely born in the London Hospital and was then taken, at the age of 2 months, for jaundice to the Queen's Hospital, Hackney. She has recently been examined, her spleen is not palpable, and at the age of 7 years she appears healthy.

*Clinical history.* The infant was born after a normal pregnancy at full term and weighed  $7\frac{1}{4}$  lb. Slight jaundice was present at birth, and this deepened during the second 24 hours. From the first the stools consisted of normal meconium, and the urine contained bile. On the second day of life she was admitted to the London Hospital, and at 12 days old she died.

On examination at 2 days old she was jaundiced to a bright lemon colour with staining of the saliva and tears; and there was much bile in the urine. She was well developed and cried normally. The spleen was palpable below the costal margin. The edge of the liver was also to be felt, but the organ was not much enlarged.

The infant sucked moderately well for the first three days in hospital. Then, losing weight, she became increasingly feeble and anaemic. The jaundice deepened and the urine still contained much bile, together with albumin, W.B.C., and R.B.C. The icterus persisted until death on the twelfth day and the stools contained bile throughout. For treatment this infant received four subcutaneous and intramuscular injections of whole blood during her first four days in hospital.

### *Laboratory findings.*

*Age.* 2nd day. Urine: Albumin 1/6 vol., many W.B.C. and R.B.C. Bile-pigments and salts present.

*Blood.* R.B.C. 3,800,000. Hgb, 85 per cent. C.I. = 1.12. Large numbers of normoblasts (34 per 100 W.B.C.). Much anisocytosis and polychromatophilia. Differential: Polymorph. neut., 72.5 per cent.; Lymphocytes, 20.5 per cent.; Monocytes, 6.0 per cent.; Myelocytes, 1.0 per cent.

3rd day. Reticulocytes, 20.4 per cent. Fragility increased, last trace of haemolysis in 0.6 per cent. NaCl.

8th day. Price-Jones curve: mean diameter =  $7.36 \mu$ .

9th day. Van den Bergh: Direct reaction = immediate strong positive. Indirect reaction = 12.5 mg. bilirubin per 100 c.c.

12th day. Blood: R.B.C., 2,400,000. Hgb, 35 per cent. C.I. = 0.74. Normoblasts, 7.5 per 100 W.B.C. Megaloblasts, 2.5 per 100 W.B.C. Anisocytosis and moderate polychromatophilia. W.B.C., 36,400. Fragility: Haemolysis up to 0.5 per cent. saline; ? trace to 0.65 per cent. Wassermann reaction negative.

*Autopsy.* P. M. 145, 1933, by Dr. A. B. Bratton, forty hours after death, at the London Hospital. (Only significant features quoted.)

*Nuclear jaundice.* Bright yellow staining of corpora Luysii ( $0.25 \times 0.1$  cm.). Well-defined opaque yellow area ( $0.2 \times 0.1$  cm.) in white matter of posterior part of right parietal lobe, 0.3 cm., from ventricular surface, surrounded by a zone (about 0.2 cm. wide) of hyperaemia. Close behind this a similar area ( $0.2 \times 0.15$  cm.) just beneath ependyma. No other jaundice of substance of brain and cord. Bright yellow staining of cerebrospinal fluid and all tissues of body, including meninges and ependyma. A little bile-stained fluid in middle ears. Yellow bile-staining of cartilaginous epiphyses of femur. Olive-brown jaundiced liver, giving a reaction for free iron somewhat masked by jaundice. Bile passages patent and containing somewhat slimy yellow bile. Slimy yellow, mixed with dark green, bile in gall bladder. Yellowish-olive jaundice of kidneys; foetal lobation of kidneys. Olive-yellow cortex and red medulla in suprarenal bodies. Somewhat enlarged spleen showing moist, red, soft, cellular pulp and small, very indistinct Malpighian bodies. Mucous catarrh and numerous streaks of altered blood in stomach. Congestion of parts of intestinal tract. A few haemorrhages in soft tissues round right common carotid artery.

*Histology.* The histology of the liver, spleen, pancreas, lung suprarenal, kidney, bone-marrow, lymph gland, heart, and brain was studied by us in sections, stained by the usual laboratory methods and also by special methods for iron and fat.

*Liver.* The columns of liver cells were widely separated, though congestion of the capillaries was not a feature. The polygonal cells showed vacuolation and degeneration of their cytoplasm and some nuclei were stained badly; there were no droplets of fat. Here and there cells were undergoing necrosis and areas of atrophy were also seen. Groups of normoblasts occurred apparently within vessels and sinusoids. Granulopoiesis was recognized by the presence of eosinophile myelocytes in the vicinity of the portal tracts. There was an extensive infiltration of the polygonal cells by bile pigment and haemosiderin. The bile-ducts appeared normal. There was neither inflammatory cell infiltration, nor fibrosis.

*Spleen.* The pulp of the spleen was congested and contained much bile pigment. The Malpighian bodies, though small, were numerous. There was haemosiderosis, but no fibrosis or reticular change. Many normoblasts and some erythroblasts were present.

*Lung.* The alveolar walls were wide and cellular, and intracapillary erythropoiesis was recognized. Normoblasts and erythroblasts were seen in the pancreas, lymph gland, and suprarenal, but erythropoiesis was not a feature of their cytology and was inconspicuous also in the kidney, where cloudy swelling of the tubular epithelium was seen with no dilatation of the

tubules. The heart-muscle showed no histological changes, and Levaditi stain for spirochetes was negative in the case of the *liver* and *suprarenal*.

*Bone-marrow.* The marrow in the lower end of the femur, relatively anaemic of matured erythrocytes, showed a uniformly active haematopoiesis with the more immature cells proportionately increased. Megakaryocytes were present in normal numbers. The osseous structures were normal and no staining of the epiphyseal cartilage persisted in the section.

*Brain.* The yellow pigment had washed out in the preparation of the sections. Two degrees of degenerative change were noted in the right parietal region and the corpus Luysii respectively. (1) In the right parietal region several small areas of complete necrosis were recognized. Their centres were destroyed and their peripheries consisted of anisotropic fat granule cells derived principally from microglia, together with fibroblasts from the neighbouring vessels, and lymphocytes (Fig. 6). There was a more diffuse proliferation of oligodendroglia and astrocytes, and at one point calcium salts appeared to have been deposited. The vessels were congested, but there was no infiltration of their perivascular spaces, and no evidence of thrombosis. The ependyma of the adjacent lateral ventricle was normal. (2) There was a partial necrosis of the whole of both of the bodies of Luys (Fig. 10). Many of their ganglion cells had disappeared, of some only a faint outline remained, and others showed vacuolation of nucleus and cytoplasm (Figs. 11, 12, 13). Large numbers of swollen astrocytes loaded with isotropic fat were seen (Fig. 15). The adjacent pyramidal tract appeared normal and the grey matter of the optic thalami was relatively unaffected. No perivascular cuffing was seen. Evidence of intracapillary erythropoiesis was noted (Fig. 14).

*Summary of changes.* 1. Partial degree of necrosis of the whole of each corpus Luysii. 2. Complete focal necrosis of small areas of white matter deep in right parietal region.

*Case 4. P. M. 173/32. 1930.*

*Female.* A case of icterus gravis neonatorum. Hare lip and cleft palate. Death at seven weeks.

*Family history.* The parents were healthy, and in the three children born earlier no severe jaundice had occurred.

*Clinical history.* This infant was born at term, birth weight of 7 lb. 14 oz. after a normal pregnancy. She was of a normal colour until she became jaundiced on the third day. She was admitted in a wasted condition at the age of one month. At this time she was jaundiced to a pale yellow colour. There was bile in both urine and faeces. The liver and spleen were enlarged one finger's breadth below the costal margin.

A test of the fragility gave the following results: trace of haemolysis in 0.39 per cent. NaCl (normal 0.42 to 0.45); incomplete haemolysis in 0.33 per cent. NaCl (normal 0.33 to 0.36). The Wassermann reaction was negative.

A blood count gave the following result: R.B.C., 4,000,000 per c.mm.; Hgb., 60 per cent.; C.I., 0.8; W.B.C., 24,000 per c.mm.

Differential: Polymorphs, 63 per cent.; Lymphocytes, 29 per cent.; Monocytes, 5 per cent.; Eosinophils, 2 per cent.; Basophils, 1 per cent.

No normoblasts or other nucleated erythrocytes were reported, but they

are likely to have been present because they were to be seen in the blood of the post-mortem sections.

By the age of 5 weeks bile had disappeared from the urine, though the baby still looked jaundiced. She died  $3\frac{1}{2}$  weeks after admission, at the age of 7 weeks.

*Autopsy.* At the autopsy, eight hours after death, the following record was made: Wasted body, slight jaundice of skin, complete cleft palate and hare lip. Brain normal. Heart: icteric staining of endocardium and intima of great vessels. Lungs: early pneumonia of right upper and middle lobes. Alimentary tract normal. Pancreas normal. Liver, green in colour, surface smooth and regular, bile-ducts patent. Spleen enlarged and firm. Suprarenals and kidneys normal.

*Histology. Liver:* The liver was studied in paraffin sections stained with haematoxylin and eosin, by van Gieson's method and by the ferro-prussiate method for iron. The capillaries were congested. On the whole the polygonal cells were fairly well-preserved, except in certain areas where they resembled the degenerate, broken-up, cells of other cases (e.g. Case 6) in showing vacuolation or cytolysis. The bile-ducts appeared to be normal. Bile-pigment was freely deposited and haemosiderosis was present. Though no polymorphs or infiltrating lymphocytes were seen, young proliferating fibroblasts were conspicuous in the portal tracts, and van Gieson's stain demonstrated an increase in the amount of periportal fibrous tissue. Many groups of developing normoblasts were seen in nests among the liver-cell columns. In the larger vessels normoblasts were in evidence as well as erythrocytes.

*Spleen.* Paraffin sections stained by the same methods showed a free deposition of bile-pigment and a very pronounced degree of haemosiderosis. The Malpighian bodies were small. Active erythropoiesis and granulopoiesis were readily distinguished, normoblasts being particularly noticeable. There was congestion of the pulp, but no alteration of the reticulum, and no evidence of fibrosis.

*Case 5. P.M. 396/31. 1929.*

*Male.* A case of icterus gravis neonatorum with very severe anaemia.

*Family history.* Parents healthy. No miscarriages, four elder children with no history of jaundice.

*Clinical history.* The jaundice appeared on the second day and death took place on the eleventh. He was a full-term baby, labour was short and easy, and he seemed healthy at birth. For the first three days the stools were said to be dark. After the onset of jaundice he became progressively weaker and paler.

On examination in hospital on the day before death he was found to be very pale and he was jaundiced to a light yellow colour. The examination of the blood, carried out by the house physician, was incomplete: Erythrocytes, 606,000, Leucocytes, 45,000, per c.mm.

The liver margin was to be felt at 1 f.b. and the spleen 2 f.b. below the costal margin. On the day after admission the stools contained bile and a specimen of urine no bile. There was no pyrexia. He died on the same day before further investigations could be carried out.

*Autopsy.* The autopsy (forty-eight hours after death) showed great anaemia, jaundice was not conspicuous. The brain was pale, the heart some-

what big, weighing 25 grm. (average at one month old = 18.2 grm.). The liver appeared normal and the bile-ducts were pervious. There were petechiae in the mucous membrane of the small intestine. The spleen was considerably enlarged. The bone-marrow, as examined in the femur and in a rib, was red throughout the shaft of the bone.

*Histology. Liver:* The histology of this organ was studied in a paraffin section stained with haematoxylin and eosin. In view of the length of time which had elapsed before fixation of the material, any opinion regarding the state of the polygonal liver cells had to be given with caution. These cells showed vacuolation and cloudy swelling, their outlines were indistinct, though their nuclei for the most part were well preserved. There was an intracellular deposition of bile-pigment. The portal tracts showed the excess of supporting tissue commonly to be seen at this age, and in this granulopoietic areas were prominent. Elsewhere, particularly in capillaries and sinusoids, there was active erythropoiesis, and in many areas this had not advanced much beyond the megaloblastic stage, though erythroblasts and normoblasts could also be distinguished in large numbers.

*Spleen.* In a paraffin section, stained with haematoxylin and eosin, the reticulum and supporting tissue appeared normal, the Malpighian bodies were small, and the splenic pulp congested. No bile-pigment was to be seen. Enormous numbers of erythroblasts and normoblasts were present, and probably megaloblasts as well, but the stain was not suitable for their differentiation.

*Bone-marrow.* A smear of the bone-marrow, stained by Leishman's method, was available in this case. This was seen to contain many large primitive basophilic cells which we believed to be megaloblasts. In addition, there were many erythroblasts and normoblasts, very few erythrocytes, some polymorphonuclear leucocytes and myelocytes, the last-named being principally of the eosinophile type. When the cells of this marrow were arranged in order of prevalence it was recognized that there was a shift to the left in the cell-pattern, particularly as regards erythropoiesis.

Case 6. P.M. 215/33. 1932.

*Male.* A case of icterus gravis neonatorum associated with haemorrhage: treated without success by injecting whole blood intramuscularly. Congenital anomaly of the right kidney.

*Family history.* Parents healthy, no family history of jaundice. Four older children, one of which was stillborn, one had physiological icterus, and one child younger than patient was healthy. No miscarriages.

*Clinical history.* He was a full-term baby, weighing 7 lb. 10 oz., and labour was normal; there was no history of any disturbance during pregnancy. The jaundice appeared six hours after birth and increased in depth. Subcutaneous haemorrhages appeared when he was seven weeks old, and four days later he was admitted to hospital.

On examination in hospital he was seen to be deeply jaundiced. There was bruising on the legs and a large bleeding haematoma on the left calf. Immediately after admission he received an intramuscular injection of 10 c.c. of his mother's blood. The liver and spleen were both enlarged, the former 2 f.b. below the costal margin. The urine contained bile but no albumin. The stools were clay-coloured. Van den Bergh's test gave a strong biphasic reaction and an indirect test totalling nine units of bilirubin. The Wassermann reaction on the baby was negative and was not done on the parents.

*Blood examination.* R.B.C., 1,800,000 per c.mm.; Hgb., 50 per cent. (Haldane's method); colour index, 1.4; Anisocytosis and poikilocytosis were noted. Nucleated red cells were present, estimated at 625 per c.mm. (= 0.03 per cent.). W.B.C., 12,500 per c.mm.

Differential: neutrophils, 41 per cent. or 5,125 per c.mm.; lymphocytes, 54 per cent. or 6,750 per c.mm.; monocytes, 5 per cent. or 625 per c.mm.; myelocytes, nil seen.

On the fourth day after admission the stools became loose, vomiting followed and dehydration appeared. He died at the age of 2 months, and a blood count on the last day was as follows: R.B.C., 3,500,000 per c.mm.; Hgb., 65 per cent. (Haldane's method); colour index, 0.9. The rise in the erythrocyte count was partly the result of dehydration. Nucleated red cells were present in increased numbers estimated at 12,880 per c.mm. (= 0.37 per cent.): W.B.C., 28,000 per c.mm.

Differential: neutrophils, 42 per cent. or 11,760 per c.mm.; neutrophile myelocytes, 1 per cent. or 280 per c.mm.; lymphocytes, 53 per cent. or 14,840 per c.mm.; monocytes, 3 per cent. or 840 per c.mm.; eosinophils, 1 per cent. or 280 per c.mm.

*Autopsy.* An autopsy was carried out forty-eight hours after death with the following findings: Wasted baby, jaundiced to a greenish-yellow colour, with subcutaneous haemorrhages and a large haematoma on the left calf. Brain pale, no staining of the basal ganglia or any part of the brain substance. Meninges bile-stained. Both middle ears contained pus. Liver enlarged, green-coloured; bile-ducts pervious; gall-bladder normal and containing green bile. Spleen enlarged, Malpighian bodies not distinguished. The kidneys were icteric and uric acid crystals were deposited in the pyramids. There was a congenital abnormality in the shape and position of the right kidney. There was some altered blood in the stomach. The medullary cavity of the femur contained marrow which was red throughout and macroscopically normal.

*Histology.* The histology of the liver, spleen, and kidney was studied by one of us (R. L.) in both frozen and paraffin sections stained with haematoxylin and eosin, by van Gieson's stain and by the ferro-prussiate method for iron, and the following report made at the time:

*Liver.* The polygonal cells of the liver showed degeneration and they stained badly. Many of them were broken up, assuming irregular shapes and sizes. Post-mortem change would have accounted for a part of these appearances. In addition the cells showed a coarse, intracellular deposit of bile-pigment, and there were bile-casts in bile-ducts and capillaries. Scattered throughout the liver were numerous normoblasts, occurring singly and in nests; a few megaloblasts and several erythroblasts were also seen. Van Gieson's stain showed delicate bands of new fibrous tissue extending outwards from the portal tracts and proliferating fibroblasts were seen in their neighbourhood. A slight degree of fine, intercellular fibrosis was appearing in the areas of maximum cell damage. Slight haemosiderosis was apparent.

*Spleen.* The reticulum looked swollen as if hyperplastic, and there was a little new fibrous tissue being laid down. There was slight haemosiderosis but no deposition of bile-pigment. Normoblasts were seen in large numbers.

*Right kidney.* The glomeruli appeared healthy, though many were of the foetal type. The epithelium of the tubules showed cloudy swelling and

post-mortem changes. Very little bile-pigment was seen. Here and there in the pyramidal region individual tubules were greatly dilated and contained blood. Normoblasts were seen in the capillaries, and among the erythrocytes in the larger vessels, but no evidence of either erythropoiesis or granulopoiesis *in situ* was obtained.

Case 7. P.M. 362/31. 1928.

*Male.* A case of icterus gravis neonatorum complicated by severe haemorrhage.

*Family history.* The parents were healthy. No previous case of icterus gravis. Three older healthy children.

*Clinical history.* Pregnancy and labour were normal, but there was a post-partum haemorrhage. The infant was normal at birth; the jaundice appeared on the second day and gradually deepened. On the fifteenth day oozing of blood from the umbilicus began. A week later the haemorrhage suddenly became severe, and he was admitted to hospital. Melaena had also occurred.

On examination in hospital he was seen to be moderately jaundiced. There was a steady loss of blood from the umbilicus. The urine contained bile. The colour of the stools was not recorded, but there was melaena on the day after admission. The weak condition of the baby did not permit any thorough examination, but it was thought that the liver and perhaps the spleen were enlarged. Local styptics having failed to arrest the umbilical haemorrhage, an whole-blood transfusion of about 200 c.c. was given, and this was followed by remarkable improvement. On the day after the transfusion the baby was again extremely anaemic. Suddenly he vomited a large quantity of blood from the mouth and nose, collapsed, and died. There was no record of any examination of the blood.

*Autopsy.* At the autopsy, twenty hours after death, the brain was icteric and there was a large haemorrhage over the left cerebral hemisphere and a small one into the pericardium. Under the pleura some bleeding had also occurred, and there was altered blood in the gastro-intestinal tract. The umbilicus did not appear to be infected, and it was surmised that the hypogastric arteries were the source of the bleeding. The liver was icteric, but not cirrhotic; the bile-ducts were patent throughout and the gall-bladder normal. The spleen was enlarged. The kidneys showed some haemorrhage into medulla and pelvis: uric acid deposits were not mentioned in the report.

*Note.* The haemorrhage over the cerebral cortex was thought by the pathologist to have arisen from a needle-puncture wound in the longitudinal sinus.

*Histology. Liver:* a paraffin section stained with haematoxylin and eosin was the only histological material available.

There was gross degeneration of the polygonal cells, which, in some areas, had proceeded to cytolysis, only the broken outlines of certain cells remaining. In the less damaged regions numerous cytoplasmic vacuolations were noted. In some of the bile-ducts and capillaries, bile-pigment was deposited in the form of droplets, and more diffusely as granules in some of the polygonal cells, particularly in cells which had been severely damaged. Throughout the parenchyma of the liver there was fairly extensive erythropoietic activity. In the portal tracts the radicles of the portal veins were dilated, the bile-ducts normal, and evidences of granulopoiesis were to be seen.

*Case 8. P.M. 271/20. 1907.*

*Female.* A case of icterus gravis neonatorum. Extensive subdural haemorrhage.

*Family history.* Parents and four older children were healthy.

*Clinical history.* The baby was born at term and was yellow at birth. For three days before admission there had been vomiting, melaena, and slight haematemesis. The stools were always coloured, and there had been no convulsions.

On admission a well-nourished baby, aged sixteen days, of bright yellow colour, the conjunctivae being affected. Liver and spleen enlarged. Bruising of left arm. After admission bruises continued to appear, there was blood in the stools and bleeding from the umbilicus, though there was no evidence of sepsis. Suddenly the fontanelle became tense and pulsated. Death ensued.

On the day before death, erythrocytes 1.57 mill. per c.mm., haemoglobin 35 per cent., C.I. 0.9, nucleated red cells 21,000 per c.mm. (101 per 100 leucocytes,—80 normoblasts, 14 megaloblasts, 7 microblasts), leucocytes 20,000 per c.mm.

Differential: polymorphs, 54 per cent.; lymphocytes, 43 per cent.; large mononuclears, 0.5 per cent.; eosinophils, 1 per cent.; basophils, 1.5 per cent.

*Autopsy.* Widespread icterus and numerous cutaneous bruises. Extensive recent subdural haemorrhage over vertex, at base, and in spinal theca. Brain soft and white, choroid plexus stained intensely yellow. Liver enlarged, dark red, and soft. Gall-bladder contained yellow bile. Spleen enlarged and soft. Kidneys: subcapsular haemorrhages, uric acid 'infarcts'. Bile and altered blood in gastro-intestinal tract; no sign of intestinal ulceration.

*Report of clinical pathologist.* A. Bacteriological: The heart blood yielded a growth of staphylococcus in one agar tube—probably a contamination. B. Pathological: Liver: Much deposit of bile-pigment in liver cells, which also show marked fatty deposit and cloudy swelling. *In most lobules are seen lines of invading inflammatory cells between the columns of liver cells.*<sup>3</sup> No fibrous tissue formation. Kidney: Congested. Capsules of glomeruli appear very cellular and crowded, but there is no evidence of nephritis.

*Case 9. P.M. 372/30. 1926.*

*Male.* A case of icterus gravis neonatorum dying after subdural haemorrhage. Early hepatic cirrhosis.

*Family history.* This infant was one of a healthy family and the parents were normal. The offsprings were arranged as follows: female, aged 10; male, aged 5; miscarriage; miscarriage three or four months; patient.

*Clinical history.* The jaundice appeared on the second day and never disappeared; death took place at the age of 6 weeks. During the third week there was passage of blood in the stool, and at 3 weeks old he was admitted for jaundice and purpura on the face and limbs. He had been a full-time baby, weighing 7½ lb., and was born normally.

On examination he was found to be a greenish-yellow baby with icteric

<sup>3</sup> We have not had an opportunity of examining the sections in this case. Erythropoietic cells in sections are not infrequently mistaken for inflammatory cells by pathologists unfamiliar with their occurrence in extramedullary sites.

mucous membranes. The stools were coloured, and the first one passed in hospital contained some bright red blood. The urine, which was acid, contained bile but no albumin or sugar. There were purpuric spots on the hands and feet, and a haematoma under the skin of the thorax on the left side. The liver and spleen were enlarged, each 2 f.b. below the costal margin, and the latter seemed to be harder than is normal. The infant's Wassermann reaction was negative.

While in hospital the jaundice increased at first, but after five days it diminished, and bile then disappeared from the urine. After three weeks there was an increase in the depth of the icterus, and the liver was estimated to be enlarged  $2\frac{1}{2}$  f.b. below the costal margin. A single convulsion occurred, and he died not long afterwards.

*Autopsy.* At the autopsy (twelve hours after death) a subdural haemorrhage was found over the brain. There was widespread icterus. The liver was enlarged, its surface smooth, and there was no macroscopic evidence of cirrhosis; it was dark green and the bile-ducts were pervious. The spleen was also enlarged. The kidneys were icteric, the cortex more than the medulla, and uric acid 'infarcts' were present: one of these organs is preserved in the pathological museum of the Hospital for Sick Children.

*Histology. Liver:* The histology of the liver was studied in paraffin sections stained with haematoxylin and eosin, by van Gieson's stain, and by Mallory's stain. The polygonal cells were, for the most part, degenerate and infiltrated with bile-pigment. Individual polygonal cells were vacuolated, and many nuclei were disappearing. The liver-cell columns were widely separated. The epithelial cells lining the bile-ducts appeared healthy. In the smallest ducts bile-casts were to be seen. The capillary vessels were congested. Numerous megaloblasts, erythroblasts, and normoblasts occurred, either in groups in the sinusoids or singly in the capillaries. No inflammatory cells were recognized. The van Gieson and Mallory sections demonstrated a fine fibrosis, particularly in the areas where most liver-cell destruction had taken place. The fibrosis was partly pericellular in type, but also encircled groups of atrophied cells, and strands of connective tissue extended from the portal tracts (see Fig. 4).

*Spleen.* The histology of the spleen was studied in 1926 by Dr. Sheldon, who reported: 'The Malpighian corpuscles are small and few in number, otherwise the spleen appears normal and is not bile-stained.' Neither the original sections nor their block being obtainable, we have not been able to study them.

*Kidney.* In a paraffin section stained with haematoxylin and eosin, we noted that the tubules were dilated, particularly their collecting portions in the medulla, and most of them were empty of casts, cells, or deposits. The cells lining the convoluted tubules contained much bile-pigment, and some of them showed cloudy swelling, while in others atrophic changes were seen. Very definite vacuolation was a feature of parts of the tubular epithelium. The majority of the glomerular tufts were normal, but some showed vacuolation of their epithelial cells. Many glomeruli were of the foetal type to be expected at this age. In some cases Bowman's capsule was dilated. There were no bile deposits in connexion with the glomeruli. The interstitial tissue and the vessels were normal, except that here and there a capillary was seen to accommodate a column of developing erythroblastic cells.

*Case 10. P.M. 362/32. 1931.*

*Male.* A case of icterus gravis neonatorum dying on the thirty-fifth day of life and showing histological evidence of commencing hepatic cirrhosis.

*Family history.* Parents healthy. Of two previous pregnancies the first was a breech with cord round neck, the child died at birth; the second was stillborn. Subsequent efforts to trace the family have failed.

*Clinical history.* He was a full-term baby, weighing  $7\frac{3}{4}$  lb., pregnancy and labour were normal. Jaundice appeared at the end of the second day or early on the third, and subsequently deepened to such a degree that on admission at the age of 17 days the skin was a dark green. The stools were at first black, then green, and latterly yellow. There was no mention of bleeding or of the colour of the urine.

On examination in hospital on the eighteenth day of life, the weight was 7 lb. 2 oz. He was as deeply jaundiced as a case of congenital obliteration of the bile-ducts. The liver was enlarged 2 f.b. below the costal margin, its surface was firm and its edge sharp. The spleen was enlarged and palpable 1 f.b. below the level of the umbilicus. There was oedema of the feet and legs, and some subcutaneous haemorrhages. Soon after admission the following investigations were carried out.

The Wassermann reaction on the blood of both mother and patient was negative. The stools contained stercobilin, and bile-pigments were in excess. The urine contained bile-pigments, bile-salts, and urobilin in excess, but no albumin or casts. Van den Bergh's test: Direct reaction—strong biphasic. Indirect reaction—9.2 units of bilirubin. Fragility of erythrocytes: Complete haemolysis in 0.33 per cent. NaCl (normal 0.33 to 0.36). Trace of haemolysis in 0.42 per cent. NaCl (normal 0.42 to 0.45).

The blood was examined cytologically on one occasion, four days after admission: R.B.C. 1,920,000 per c.mm.; Hgb. 35 per cent. (Haldane's method); Colour index 0.9; anisocytosis, polychromasia, and punctate basophilia were noted, and there were numbers of nucleated red cells, estimated at 6,318 per c.mm. (= 0.33 per cent.); W.B.C. 11,700 per c.mm.; Differential: neutrophils 23 per cent. or 2,691 per c.mm.; neutrophile myelocytes 3 per cent. or 351 per c.mm.; eosinophils 1 per cent. or 117 per c.mm.; eosinophile myelocytes 1 per cent. or 117 per c.mm.; lymphocytes 65 per cent. or 7,605 per c.mm.; lymphoblasts 1 per cent. or 117 per c.mm.; monocytes 6 per cent. or 702 per c.mm.

In the second week of his stay in hospital, a gastro-intestinal infection seems to have been acquired; rapid loss of weight; persistent vomiting, and severe diarrhoea ended in death at the age of 5 weeks.

*Autopsy.* At the autopsy (six hours after death) it was observed that the infant was jaundiced to a dark green colour, wasted, and dehydrated. The brain was normal, and no staining of the basal nuclei was noted. The heart was larger than normal for the age, the wall of the left ventricle being thicker than the right. There was terminal pneumonia. The gastro-intestinal tract showed no abnormalities. The liver was enlarged, soft, and dark green in colour; there was no perihepatitis. The gall-bladder was normal and contained green bile. The bile-ducts were pervious. The spleen was two or three times the normal size for the age, there was no perisplenitis; on section its substance was firm and dark, and no Malpighian bodies were discernible. Under the capsule, and bulging it out, was an old encapsulated haemorrhage as big as a cherry stone. The kidneys contained linear uric acid deposits in the pyramids converging towards their apices,

and the cortex was icteric. There was a small amount of yellow, ascitic fluid in the peritoneum. The bone-marrow was not studied.

*Histology. Liver:* Paraffin sections were stained with haematoxylin and eosin by van Gieson's method and for iron; and a routine report was made by one of us (R. L.) at the time. The outstanding features of the sections were widespread degenerative changes in the polygonal cells, deposition of bile-pigment and intercellular fibrosis. No erythropoiesis or granulopoiesis were recognized, even after a careful search. Groups of liver cells were seen broken up into islets, separated by developing fibrous tissue and young fibroblasts. Many liver cells were infiltrated with bile-pigment, vacuolated, atrophic, or showing nuclear karyorrhexis. Massive haemosiderosis had occurred in them. The fibrosis was widespread and recent, and condensations had occurred round the portal tracts and central veins, but its presence was most obviously pathological in separating or replacing the cell-columns.

*Spleen.* Stained by haematoxylin and eosin the reticular tissue of the spleen looked denser than normal, the venous sinuses and blood spaces were congested, and the Malpighian bodies small and inconspicuous. No haematopoiesis was evident. The encapsulated haemorrhage, noted at the autopsy, was not recent, and specks of calcification were noted in its peripheral parts. A van Gieson stain showed thickening of the splenic capsule and fibrosis, affecting, not only pre-existing fibrous connective tissue, but also occurring as a diffuse reticular change (Fig. 9). Bile-pigment and haemosiderin were present.

*Case 11. P.M. 25/32. 1929.*

*Male.* A case of icterus gravis neonatorum progressing to lobular cirrhosis.

*Family history.* The mother had 'kidney trouble' during the pregnancy; apart from this the parents were both healthy. The patient was a first child, and there had been two subsequent pregnancies. One of these was a miscarriage at four months, and the other normal, the child being 2 years old. Their paternal uncles had had attacks of jaundice, but attempts to get them to hospital were unsuccessful.

*Clinical history.* Jaundice was said to have been present from birth and the stools almost colourless throughout. He was admitted to hospital at the age of 3 months, and died twelve days later. He was a full-time baby, and weighed 6½ lb. at birth. Labour was long and instruments were used.

On examination in hospital he was described as fairly well nourished and moderately jaundiced. There was bile in the urine and no albumin. The liver and spleen were each enlarged about 2 f.b. below the costal margin. The stools were faintly coloured, and the following observations were recorded:

Split fat	.	.	.	.	.	67.18	} per cent. of dried faeces.
Unsplit fat	.	.	.	.	.	5.72	
Total fat	.	.	.	.	.	72.9	

The guiac test was positive and a weak haematoporphyrin spectrum was present; stercobilin and bile-pigments were absent. The Wassermann reaction was negative. Van den Bergh's test: Direct reaction: biphasic reaction. Indirect reaction: 6 units of bilirubin (normal 0.2 to 0.6 units). Fragility test: Incomplete haemolysis at 0.33 per cent. NaCl (normal = 0.33

to 0.36 complete). Trace of haemolysis at 0.39 per cent. NaCl (normal = 0.42 to 0.45). There was no blood count and no microscopical examination of the blood.

During his stay in the hospital ward it is probable that he acquired some infection, for the temperature was elevated on the fourth day, and soon after this diarrhoea appeared, and then persistent vomiting. Just before death there was profuse haemorrhage from the nose and mouth, but previously there had been no manifest haemorrhage or purpura.

*Autopsy.* At the autopsy (thirty-six hours after death) the body was found to be emaciated and deeply jaundiced. The brain was described as 'icteric throughout', and there was no haemorrhage. There was pus in the left ear. The liver was olive-green and did not show macroscopic evidence of fibrosis. The gall-bladder was normal and contained green bile, which could be squeezed without difficulty into the duodenum. The bile-ducts appeared normal. The spleen, apart from being enlarged, presented no macroscopic abnormality. The kidneys were icteric and showed uric acid deposits.

*Histology. Liver:* The histology of the liver was studied in paraffin sections stained with haematoxylin and eosin and by Mallory's stain. The polygonal cells showed considerable degenerative change with cytoplasmic vacuolation and diminished staining affinity on the part of their nuclei. These changes were due, in part at least, to post-mortem effects. The liver cells contained much bile-pigment. There was a well-advanced cirrhosis of mixed type, the fibrous tissue strands surrounding individual cells and groups of cells. In many areas this fibrous tissue had condensed into loose fibrous nodules, the meshes of which contained the remnants of atrophied liver cells, a few infiltrating inflammatory cells, and some young fibroblasts (Fig. 4). Condensations of fibrous tissue also occurred in the region of all vessels and portal tracts, and in such situations eosinophile myelocytes, indicative of granulopoiesis were distinguished. The bile-ducts were patent, and many of them contained bile-casts. No pseudo-bile canaliculi were seen.

*Spleen.* We examined paraffin sections stained with haematoxylin and eosin, and with methylene blue and eosin, and found that there was a diffuse fibrosis of this organ and probably some degree of hyperplasia of the reticulum. The Malpighian bodies were very small, the capsule thickened, and bile deposits were present. Some developing blood-cells, both normoblasts and myelocytes, were seen, but not in great numbers.

*Case 12. P.M. 230/32. 1930.*

*Male.* A case of jaundice arising during the fourth week and ending fatally. Perilobular cirrhosis. Subdural haemorrhage.

*Family history.* One older child, a female, aged 3, healthy. An attempt has been made to trace parents, but up to the time of writing without success, and there is no subsequent information about the family. There were no miscarriages.

*Clinical history.* The patient was a full-time baby weighing 7 lb. 9 oz. Labour was normal. At the age of 3 weeks melaena was observed for a period of three days, and vomiting also occurred. Four days after the onset of the melaena the baby was noticed to be jaundiced; the stools were green, slimy, and offensive.

He was admitted to hospital at the age of 1 month, and on examination was found to be a well-nourished, jaundiced, and afebrile baby. The liver

and spleen were said not to be palpable (clinical clerk's note). The urine contained bile and a trace of albumin. The Wassermann reaction was negative. The stools were yellow. Analysis:

Split fat . . . . .	49.41	} per cent. of dried faeces.
Unsplit fat . . . . .	23.14	
Total fat . . . . .	72.55	

Microscopically: Excess of fat globules and a few fatty acid crystals.

Van den Bergh's test: Direct reaction: positive. Indirect reaction: 5.5 units bilirubin.

A clinical diagnosis of catarrhal jaundice was made. Gradually the icterus became deeper, and sixteen days later he passed into convulsions and died from cerebral haemorrhage at the age of 7 weeks. There was no cytological examination of the blood during life, but histological sections provided opportunities for recognizing the presence of nucleated erythrocytes in the blood-stream.

*Autopsy.* A post-mortem was carried out twelve hours after death, with the following findings:

The body was that of a well-nourished infant, deeply jaundiced. There were no haemorrhages into the skin. The cerebrospinal fluid was blood-stained, and a haemorrhage, the size of a tangerine orange, was found over the left parietal lobe; there was no sign of trauma. The brain was slightly icteric, but otherwise normal. The heart was large, weighing 30 gm. (normal 18–20 gm.), and there was a small epicardial haemorrhage over the right ventricle. The liver was enlarged, weighing 250 gm. In colour it was a dark greenish-yellow; there was no macroscopical evidence of cirrhosis. The bile-ducts were patent and the gall-bladder normal. The lymphatic glands in the portal fissure were slightly enlarged. The spleen appeared normal and weighed 20 gm. There was bile-staining of the kidneys and haemorrhage into the left renal pelvis. There was a retro-peritoneal haemorrhage in the left loin.

*Histology. Liver:* Material—paraffin sections, stained with haematoxylin and eosin, by van Gieson's and by Mallory's methods. The polygonal cells stained badly and were degenerate, showing vacuolation and cytolysis. The bile-ducts appeared to be normal. Bile-pigment was freely deposited as fine granules in the cells and as droplets in bile capillaries. There was slight haemosiderosis, and many Küpffer cells were stained brown by the haematoxylin and eosin. Normoblasts occurred singly and in groups. Nests of erythroblasts, showing mitoses, and a few megaloblasts were distinguished. In the region of the portal tracts, normoblasts and several eosinophile myelocytes were recognized, together with polymorph leucocytes.

The fibrous tissue stains demonstrated intercellular fibrosis and some increase of fibrous tissue around the portal tracts and vessels. The fibrosis among the polygonal cells seemed especially related to atrophic areas and to islands of erythropoiesis. The histological picture resembled that of Case 11 (Fig. 4), and might be classified as an early perilobular cirrhosis.

*Spleen.* In a paraffin section stained with haematoxylin the reticulum appeared normal and the capsule slightly thickened. The Malpighian bodies were small, clearly defined, and increased in number. Erythropoiesis was recognized by the presence of erythroblasts and normoblasts, and granulopoiesis by eosinophile myelocytes and eosinophile polymorphs. No bile was seen, and an iron

stain showed slight haemosiderosis. Van Gieson's stain demonstrated an increase of young fibrous tissue.

*Kidney.* A paraffin section stained with haematoxylin and eosin showed the following histology. In the cortical region the capsule was normal and some of the tubules dilated. There were many foetal glomeruli and about a quarter of Bowman's capsules were dilated. No erythropoiesis was recognized. In the medullary region the tubules were dilated and granules of bile-pigments were deposited in some of the epithelial cells.

*Blood.* The contents of the veins in a section of the spleen provided an opportunity for noting some of the blood-cells present *post mortem*. In addition to erythrocytes and leucocytes both normoblasts and erythroblasts were recognized.

*Case 13. P.M. 378/33. 1933.*

*Male.* A case of icterus gravis neonatorum treated with human blood-serum intramuscularly, too late to avoid death from a gastro-intestinal infection: developmental abnormality of lungs. Probably spastic diplegia; intracranial haemorrhage.

*Family history.* Parents healthy. Two older children, both well. No history of jaundice in parents or relations.

*Clinical history.* The baby was born at full time, and there was no history of any disturbance of the mother's health during pregnancy. The baby was pale at birth and 'looked like marble'. Within forty-eight hours he was deeply jaundiced. At death, at the end of five weeks, he was still icteric, but the jaundice was then diminishing.

He was seen in hospital on the eighteenth day. At this time the liver and spleen were enlarged. Both urine and faeces contained bile. Van den Bergh's test:—Direct: positive biphasic reaction; indirect: 7.5 units of bilirubin. No albuminuria. There was no purpura. Bleeding time 6 min., coagulation time 2 min. 42 sec. For haematological findings see Chart 1. Fragility of erythrocytes: Complete haemolysis in 0.30 per cent. NaCl (normal 0.33 per cent.). Trace of haemolysis in 0.42 per cent. NaCl (normal 0.39 per cent.). Blood-serum calcium 11.1 mg. per cent. (normal 10–11). Wassermann reaction negative. The head was retracted and the legs were spastic, suggesting the diagnosis of diplegia.

Price-Jones curves showed megalocytosis and subsequently a rapid return towards the normal. There was increased variability, and microcytes occurred as well as megalocytes.

Soon after admission to hospital the temperature became elevated, reaching 104.4° F. on the fourth day. At the same time the stools became loose, and later vomiting added to the gravity of the case. 10 c.c. of the father's blood-serum was given into the buttock without obvious benefit. A further period of fever, accompanied by dehydration, ushered in the fatal termination.

*Autopsy.* A wasted, icteric baby, with staining of all tissues except the brain. Basal ganglia normal; recent, bilateral, subdural, ante-mortem haemorrhage over vertex. Heart normal except for icterus. Liver enlarged, firm, and green. Bile-ducts and gall-bladder normal. Spleen slightly enlarged, red, and homogeneous on section. Kidneys pale and yellow-coloured; linear striations, the colour of cayenne pepper, were seen in

CHART 1. Case 13. Haematological Findings

Date.	R.B.C. in millions per c.mm.	Haemoglobin % (Haldane).	C.I.	Nucleated erythrocytes per c.mm.	Erythroblasts per 100 W.B.C.	Normoblasts per 100 W.B.C.	Reticulocytes per 100 R.B.C.	W.B.C. per c.mm.	Polymorphs %.	Myelocytes %.	Lymphocytes %.	Monocytes %.	Eosinophils %.	Basophils %.	Remarks.
2.2.33	2.23	52	1.18	7,200	1.5	28	11	16,700	56	1	37.5	5	0	0.5	Polychromasia, anisocytosis platelets reduced
7.2.33	2.73	54	1.0	1,800	0.5	15.5	9.6	11,250	45.5	0.5	49.0	3.5	1.0	1.0	—
15.2.33	4.00	68	0.85	351	0	3	4.5	11,700	33.5	0.5	53.0	8.5	4.0	0	Türk cells 0.5 % Polychromasia +++

the pyramids; presumably these were pigmented uric acid deposits. Towards the apices of the pyramids these deposits had produced local necrosis with the formation of cavities. Bone-marrow bright red in all the bones examined (ribs, sternum, femur). Pus in middle ears. Lungs presented developmental abnormalities: four lobes on right side, three on left. The accessory left lower lobe was atelectatic and honeycombed by congenital bronchiectasis.

*Histology. Liver:* Paraffin sections stained with haematoxylin and eosin showed granular degeneration and fatty change in the polygonal cells, capillaries congested and normoblasts visible in them, deposition of bile-pigment. Groups of erythroblasts and normoblasts in liver sinusoids. The ferro-prussiate reaction showed iron granules in the cells. Bile-ducts healthy. There were areas of early fibrosis with scanty young fibroblasts distributed, particularly in relation to the portal tracts and vessels. The appearances suggested replacement fibrosis either of destroyed liver cells or of disappearing blood-forming islets (van Gieson's stain).

*Spleen.* The presence of erythroblasts and normoblasts indicated erythropoietic activity, and of myelocytes, granulopoiesis. The Malpighian bodies were minute. A small amount of iron was demonstrated and some bile-pigment.

*Aorta.* Here and there the intimal lining showed swelling and degeneration; a patch of sub-intimal proliferation with (?) oedema was seen. No other changes.

*Kidneys.* For the most part the cortex was normal; foetal glomeruli and foetal tubules were present. In the medulla degenerated cystic areas, produced by the coalescence of greatly dilated tubules, were seen, and the surrounding renal tissue was compressed. No haemosiderosis.

*Lungs.* Summary of report: 'The parenchyma of the affected lobe combines the appearances of atelectasis and extreme emphysema. Some of the bronchi are greatly dilated without evidence of inflammation, others are small and compressed (congenital atelectatic bronchiectasis).'

*Bone-marrow.* The preservation of the tissue was unsuitable for cytological studies.

*Case 14. P.M. 413/33. 1933.*

*Female.* A case of icterus gravis neonatorum. Recovery after blood transfusions. Died of pertussis and pneumonia after recovery from jaundice and anaemia.

*Family history.* Parents healthy. There had been one previous child who had been normal until her death from influenza at 2 years old. No miscarriages.

*Clinical history.* Full-time female child, 6 lb. at birth, and delivered normally. Jaundice appeared two days after birth and subsequently deepened. She was admitted to hospital on the fourteenth day of life.

On examination she was found to be a well-nourished baby with anaemia, breathlessness, and jaundice. The liver and spleen were enlarged. Bile was present in stools and urine. Van den Bergh's test gave a positive direct reaction and 11 units of bilirubin by the indirect test. Examination of the blood showed only 800,000 erythrocytes per c.mm. and 18 per cent. of

CHART 2. Case 14

Date.	R.B.C. in millions per c.mm.	Hgb. % (Haldane).	Ct.	Haematocrit %.	Reticulocytes % of R.B.C.	Nucleated erythrocytes per c.mm.	Erythroblasts per 100 W.B.C.	Normoblasts per 100 W.B.C.	W.B.C. per c.mm.	Myeloblasts % W.B.C.	Myelocytes % W.B.C.	Polymorphs %.	Lymphocytes %.	Monocytes %.	Eosinophils %.	Basophils %.	Turk cells %.	Van den Bergh reaction (direct).	Van den Bergh reaction (indirect) (units bilirubin).	Blood transfusions (c.c.).	Remarks.
9.3.33	0.80	18	1.1	10	—	925	0	2.5	36,950	—	1	63	31.5	3.5	0.5	0.5	0	+	11	50	Count taken before transfusion in each case.
10.3.33	2.50	51	1.0	—	6.8	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
15.3.33	0.724	15	1.0	9	20.2	5,330	5.6	34.8	13,112	0.8	2.4	49.6	38.4	4.0	4.4	0.4	0	—	—	65	Platelets 9,412 c.mm. also on 15.3 P.B.; P.; A.; Pk.
16.3.33	1.55	20	0.7	21	16	7,200	3.5	33.5	19,720	—	2.0	60	29.5	6	2.5	0	0	—	—	—	—
18.3.33	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	+	5	—	—
																		weak biphasic			
20.3.33	2.00	40	1.0	—	—	34,000	4.0	75	40,000	0	0	42	47	3	7	1	0	—	—	—	P.B.; P.; A.; Pk.
24.3.33	2.796	45	0.8	32	11.7	7,467	2.5	23.5	28,700	0.5	0.5	33.5	57	6.5	0.5	1	0.5	—	—	—	P.B.; P.; A.; Pk.
29.3.33	2.5	53	1.1	26	11	271	0.5	2	10,850	0	2	39.5	47.5	8.5	2.5	0	0	—	—	—	P.B.; P.; A.
6.4.33	2.83	63	1.1	—	9.3	925	—	2.5	19,000	0	0.5	42.5	49	4.5	2	1	0.5	—	—	—	A.
12.4.33	1.98	44	1.1	—	10.3	0	0	0	19,350	0	0	15	78	5	2	0	0	—	—	—	—
13.4.33	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	120	—
25.4.33	4.8	79	0.8	—	4.6	0	0	0	33,400	0	0.5	24	63.5	8.5	2	1	0.5	—	—	—	Wh. Cough.
																					Pk. = Poikilocytosis.
																					P.B. = Punctate basophilia. A. = Anisocytosis. P. = Polychromasia. Pk. = Poikilocytosis.

P.B. = Punctate basophilia. A = Anisocytosis. P = Polychromasia.

haemoglobin (Haldane). A blood transfusion was carried out. Both the father's and mother's bloods were compatible by direct matching, and the father's blood was chosen, 50 c.c. being given with great benefit. On the day following the transfusion the degree of jaundice was increased, but the blood count was improved (see Chart 2). The baby was discharged from hospital and the blood examined a week later. A second blood transfusion was deemed advisable, 65 c.c. of the father's blood being given. On the day following the second transfusion the jaundice was again somewhat deeper. Bilirubinuria continued, and the spleen and liver remained enlarged. Van den Bergh: Direct reaction = weak biphasic. Indirect test = 5 units. A third transfusion of 120 c.c. was required a month after the first.

Gradually clinical recovery was obtained. At the age of 2 months the infant contracted pertussis, which ended fatally with broncho-pneumonia two weeks later.

(For the haematological findings in the case see Chart 2.)

No autopsy was obtainable in this case beyond the histological examination of the liver, spleen, and bone-marrow.

*Histology. Liver:* A paraffin section of the liver stained with haematoxylin and eosin showed fatty changes in the liver cells associated with the toxæmia of the terminal pneumonia. The portal tracts were normal, and the capillaries slightly congested. A few normoblasts were to be seen. No deposits of bile-pigment. Stained by van Gieson's method no fibrous tissue, excessive for the age, was seen. Haemosiderosis was present.

*Spleen.* A paraffin section of the spleen, stained by haematoxylin and eosin, showed a splenic pulp normal except for the deposition of pigment and haemosiderosis. The Malpighian bodies were small, and most of them contained a core of non-cellular eosinophilic material. A few normoblasts were visible. By this stain and by van Gieson's method the reticulum was abnormally dense. Some slight, diffused fibrosis was seen.

*Bone-marrow (Rib).* A fixed smear, stained with Leishman, and a section stained with haematoxylin and eosin after decalcification of tissue were examined. The epiphyseal cartilage, epiphyseal line, periosteum, cortex, and spongiosa were normal. Erythropoiesis was very active, the majority of the cells being at a stage earlier than the normoblast, and mature erythrocytes were scanty. Active granulopoiesis was evidenced by the presence of numerous myeloblasts and myelocytes, both eosinophilic and basophilic. Megakaryocytes were seen in increased numbers.

#### *Case 15. M.D.*

*Male.* A case of icterus gravis neonatorum. Recovery after blood transfusions. ? Intracranial haemorrhage.

*Family history.* Parents healthy. There had been one previous child, always healthy and never jaundiced.

*Clinical history.* Pregnancy was normal and went to term. Nothing abnormal was noticed by the doctor in attendance concerning the placenta, liquor amnii, or vernix caseosa. Labour was normal. The infant was jaundiced at birth. The icterus diminished for eight days and then deepened again. The stools showed the changes to be expected in the newly-born, and were yellow at the time of admission to hospital. Bilirubinuria had been observed.

On examination on the eleventh day the baby was found to be well-nourished, afebrile, and drowsy. The face and body were equally and deeply jaundiced to an orange colour. The mucous membranes were also affected. Urine: acid, trace of albumin, urobilin present, bile-pigments present, bile-salts absent, and chlorides reduced. Stool was yellow and contained bile-pigment but no stercobilin. The heart was not enlarged, and there were no nervous changes. There was splenomegaly, hepatomegaly, and obvious anaemia. Examination of the blood: erythrocytes, 1,400,000 per c.mm., 30 per cent. haemoglobin (Haldane), erythroblastaemia, and reticulocytosis 11.9 per cent. The father was selected as a donor (direct matching) and an immediate transfusion of 100 c.c. was beneficial (see Chart 3). He was discharged from hospital the next day.

Following the initial transfusion the icterus persisted, and ten days subsequently a second transfusion (100 c.c. as an out-patient, same donor) was indicated by a falling blood count. When he reached the age of 31 days the icterus was considerably diminished both to clinical observation and by the quantitative van den Bergh reaction. From this time the colour became steadily lighter, the spleen remaining palpable. On the thirty-sixth day of life an attack of convulsions was accompanied by a sudden return of the icterus, and he was readmitted to hospital looking very ill. The spleen was of the same size as previously. The skull was tense, the sutures separated, and the fontanelle bulging. The anaemia had increased with the jaundice. Vomiting occurred at intervals. Spontaneous intracranial haemorrhage was diagnosed, and a third transfusion (100 c.c., same donor) was performed with clinical and haematological benefit. Subcutaneous salines were employed on the two following days.

The subsequent course to recovery was uneventful, and when seen in his tenth week he looked a normal baby, the anaemia disappeared, the signs of intracranial disturbance gone, sutures closed, fontanelle normal, no spasticity, mentality and reflexes normal for the age. The liver was not enlarged and the spleen was shrinking. To prevent the occurrence of iron-deficiency anaemia, a course of sugar of iron was ordered. At the age of 4 months he was in perfect health, and the only abnormality was a firm palpable spleen (about 1 f.b.), which had disappeared at six months.

*Additional pathological data* (see also Chart 3)

Van den Bergh reactions:

<i>Date.</i>	<i>Immediate Direct Reaction.</i>	<i>Indirect Test.</i>
18.5.33	Strongly positive	35 units bilirubin
29.5.33	Strongly positive	44 units bilirubin
6.6.33	Positive	32 units bilirubin

*Fragility.* Just incomplete haemolysis in 0.30 per cent. NaCl.

Trace of haemolysis in 0.39 per cent. NaCl.

22.5.33

*Normals.*

Inorganic blood phosphorus	3.6 mg. per cent.	4 to 5.5 mg. per cent.
Blood uric acid	2.7 mg. per cent.	2 to 4 mg. per cent.
Blood phosphatase	15.7 units	5 to 20 units
Blood urea	25 mg. per cent.	15 to 40 mg. per cent.
Blood cholesterol	154 mg. per cent.	100 to 200 mg. per cent.

CHART 3. Case 15

Date.	R.B.C. in millions	Hgb. % (Haldane).	G.I.	Haematocrit %.	Reticulocytes % of R.B.C.	Nucleated erythrocytes per cmm.	Erythroblasts per 100 W.B.C.	Normoblasts per 100 W.B.C.	W.B.C. per cmm.	Myeloblasts per 100 W.B.C.	Myelocytes per 100 W.B.C.	Polymorphs W.B.C.	Lymphocytes %.	Monocytes %.	Eosinophils %.	Basophils %.	Türk cells %.	Van den Bergh reaction (direct).	Van den Bergh reaction (indirect) (units bilirubin).	Blood transfusions (c.c.).	Remarks.
Born 5.5.33																					
18.5.33	1.4	30	1.07	14	11.9	6,680	1.5	18.5	32,900	0	0.5	40.5	52	5.5	1.5	0	0	+	35	—	Platelets per cmm. 572,600.
19.5.33	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	100	—
20.5.33	2.8	58	1.04	26.5	13.5	5,300	3	65.5	11,300	0.5	2.5	30	57	8.5	0.5	1	0	—	—	—	Bile-pigments in stool. No stercobilin detected. P.B. + A. + + P. + + +
29.5.33	2.4	45	0.94	—	34	3,328	2	14	20,800	1	0.5	36	59.5	2	1	0	0	+	44	100	Fragility of R.B.C. 0.3 %, 0.39 %, P. + + + P.B. +
6.6.33	3.46	55	0.8	—	8.9	1,402	1.5	6.5	17,400	0	0	22	70	4.5	3.5	0	0	+	32	—	—
12.6.33	2.88	54	0.96	—	5.5	258	0.5	1	17,200	0	0	64	25.5	7.5	1.5	1	0.5	—	—	—	—
13.6.33	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	100	—
14.6.33	3.68	90	1.25	—	8.1	790	0	4	19,750	0	0	30	58.5	6.5	3.5	1.5	0	—	—	—	Subcutaneous saline.
15.6.33	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	Subcutaneous salines.
24.6.33	3.31	75	1.13	—	7.7	0	0	0	8,800	0	0	16.5	78.5	3	1.5	0	0.5	—	—	—	P.B. +
3.7.33	4.69	76	0.82	—	10.0	0	0	0	14,000	0	0	7.5	81.5	3	7.5	0	0	—	—	—	—
13.7.33	5.55	86	0.78	—	5.3	0	0	0	19,850	0	0	7.0	82	8	3	0	0	—	—	—	P.B. +
31.7.33	4.90	90	0.91	—	17.5	0	0	0	—	—	—	—	—	—	—	—	—	—	—	—	—
P.B. = Punctate basophilia. P. = Polychromasia. A. = Anisocytosis.																					

P.B. = Punctate basophilia.

P. = Polychromasia.

A. = Anisocytosis.

Case 16. G.B.

*Male.* A case of icterus neonatorum with anaemia. ? Due to excessive haemolysis in a premature infant, but with a family history suggesting icterus gravis neonatorum and thus on the border-line between icterus gravis and icterus simplex. Recovery after blood transfusions.

*Family history.* Parents healthy. Blood Wassermann reactions negative in both. There had been six pregnancies. The first resulted in a stillborn child at the sixth month (malformed placenta). The second, third, and fourth were miscarriages. The fifth resulted in a male child six weeks premature, icteric on the second day and died on the third day. The sixth pregnancy produced the patient, three weeks premature, who became icteric on the third day. The doctor who had looked after the family could not recall anything unusual about the liquor amnii, vernix caseosa, or placenta in any instance.

*Clinical history.* Labour was normal, nothing abnormal was noted regarding the liquor amnii, vernix caseosa, or placenta. Icterus appeared during the third day, and he was brought to hospital when 3 weeks of age on account of deep jaundice.

On examination he was a well-nourished drowsy baby, deeply jaundiced to an orange colour. The liver was palpable, but not judged to be enlarged. The spleen was not felt.

Urine: acid; albumin, sugar, acetone bodies absent; urobilin present, bile-pigments present; bile-salts absent; chlorides diminished, no cells or casts. The stool contained bile-pigments; no stercobilin could be detected. Microscopically there was an excess of fat. Van den Bergh test: direct reaction strongly positive; indirect test = 28 units of bilirubin. Blood: anaemia with reticulocytosis (see Chart 4).

This infant was successfully treated as an out-patient. On May 4th (3 weeks old) he was brought up to the hospital and received a whole blood transfusion of 70 c.c. of paternal blood. On May 11th 50 c.c. were given. Subsequently the degree of anaemia did not demand further transfusions. The icterus persisted for eight weeks. When no longer jaundiced he received a course of iron, and he has remained well up to the time of writing this paper.

Case 17. M.A.

*Male.* A case of haemolytic anaemia associated with icterus, originating in the neonatal period, and passing gradually into the syndrome of von Jaksch's anaemia.

(Clinical notes from University College Hospital.)

*Family history.* Parents alive and well. One brother healthy.

*Clinical history.* The patient, a male infant, was admitted to University College Hospital, at the age of  $5\frac{1}{2}$  months, for increasing anaemia and abdominal tumour. Labour had been normal, and he weighed 9 lb. He was noticed to be pale from birth and remained pale. Sometimes yellowness of the skin and conjunctivae appeared, passing off in a few days, only to return on subsequent occasions. A left-sided tumour (spleen) had been discovered six weeks before admission. Feeding had been by the breast. The stools and urine were reported as normal, the appetite good, and vomiting occasional. He had gained weight slowly from birth.

CHART 4. Case 16

Date.	R.B.C. millions per c.mm.	Haemoglobin % (Haldane).	C.I. 1-25	Nucleated erythro- cytes per c.mm.	Erythroblasts per 100 W.B.C.	Normoblasts per 100 W.B.C.	Reticulocytes per 100 R.B.C.	W.B.C. per c.mm.	Polymorphs %.	Myelocytes %.	Lymphocytes %.	Monocytes %.	Eosinophils %.	Basophils %.	Transfusions.	Remarks.
2.5.33	2.00	50	1.25	None seen	0	1	3	19,650	41	0	73	2.5	3	0	70 c.c. father's blood	Van den Bergh, direct ++ indirect, 28 units
4.5.33	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	Bilirubinuria
5.5.33	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	Better. Less jaundiced
6.5.33	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	More jaundiced
10.5.33	2.32	50	1.1	196	0	1	3	19,650	41	0	73	2.5	3	0	—	Polychromasia of R.B.C. Gained weight; more jaundiced. Bile in stool and urine
11.5.33	—	—	—	—	—	—	—	—	—	—	—	—	—	—	50 c.c. father's blood	—
17.5.33	3.1	60	0.96	128	0	1	4.5	12,800	22.5	0	60	10.5	6	1	—	Gaining weight, less jaun- dice. Urine less dark
24.5.33	3.39	62	0.93	None seen	0	0	5.6	9,300	29	0.5	66.5	1.5	2.5	0	—	Less jaundice
7.6.33	3.60	75	1.04	0	0	0	—	7,850	—	—	—	—	—	—	—	Very little jaundice. Ferri carb. sacch. gr. ii t.d.s.
5.7.33	4.09	80	1.0	0	0	0	1.7	9,200	21	0	68	2	7	1	—	Well
2.8.33	4.8	84	0.87	0	0	0	0.3	8,600	—	—	—	—	—	—	—	Looks very well. Treat- ment stopped

On examination he was found to be pale, well nourished, and slightly jaundiced, the conjunctivae being involved as well as the skin. The respiratory, cardiovascular, and nervous systems were normal. Abdomen protuberant, spleen enlarged, with its lower border extending down to the left iliac crest. Liver edge 3 f.b. below costal margin. No ascites. No enlargement of lymphatic glands. The Wassermann reaction was negative. No record of chemical tests on urine. (Blood picture, see Chart 5). Physician's diagnosis, 'Congenital anaemia'.

From the date when he first came under observation until he died at the age of 8½ months, he was in hospital on three occasions, and was treated by blood injections, blood transfusions, bone-marrow, and iron therapy. The blood injections and transfusions, with their results, may be seen in Chart 5.

During the period of observation the anaemia varied between a minimum of 1.2 million erythrocytes (Hgb 17 per cent.) to a maximum of 4.65 millions (Hgb 56 per cent.). The erythroblastemia, splenomegaly, and hepatomegaly persisted. During the latter stages of the illness the clinical picture assumed the characters of so-called von Jaksch's anaemia which, indeed, became the physician's diagnosis, and as time went on the spleen was observed to harden as it diminished in size, and slight but varying degrees of icterus were present at times.

*Autopsy.* Heart enlarged with hypertrophy of left ventricle. Lungs normal. Spleen much enlarged and firm, red in colour on section, with areas of fibrosis; Prussian-blue reaction positive, showing the presence of large quantities of iron. Liver enlarged, Prussian-blue reaction strongly positive. Kidneys: exaggerated differentiation between cortex and medulla; cortex dark red and showing the presence of iron with potassium ferrocyanide. In the tibia and femur the bone-marrow was bright red throughout the shaft; this is normal for the age. Intestine, mucous membrane gave slight Prussian-blue reaction. Brain and meninges normal. Bilateral otitis media.

*Histology. Liver:* the polygonal cells were undergoing cytolysis. Individual cells showed coagulative necrosis, vacuolation, and fatty degeneration. A more advanced stage was represented by the disappearance of the cytoplasm leaving fragmented nuclei. The vessels and bile-ducts were normal. Numbers of normoblasts were seen in the capillaries (haematoxylin and eosin stain).

*Spleen.* The sinuses were engorged with blood. In places there were non-fibrotic, hyaline areas, suggesting old infarcts or haemorrhages (haematoxylin and eosin stain). By contrast, and as a result of the vascular engorgement, the supportive tissue seemed little in evidence, and there was no increase of fibrous tissue; the Malpighian bodies were reduced in size (van Gieson stain).

*Bone-marrow.* Studied in haematoxylin and eosin preparation, this bone-marrow showed a great preponderance of very immature cells of the erythrocyte series (megablasts); there were relatively few intermediate cells acquiring haemoglobin (erythroblasts) and still fewer normoblasts. Matured erythrocytes were scanty (so-called 'megablastic' bone-marrow (Sabin)).

Areas of fibrosis, possibly the result of haemorrhage or of some toxin (?), were present (van Gieson stain).

CHART 5. Case 17

Date.	R.B.C. in millions per c.mm.	Hgb %.	C.I.	Retic. %.	Nucleated R.B.C. per c.mm.	Abnormalities in R.B.C.	W.B.C. per c.mm.	Myelocytes %.	Myeloblasts %.	Polymorphs %.	Lymphocytes %.	Monocytes %.	Eosinophils %.	Basophils %.	Fragility of R.B.C.	Van den Bergh direct.	Van den Bergh indirect.	Transfusions.	Injections.	Remarks.
19.1.32	1.20	17	0.70	—	13,500	Poly- chromasia P. Baso- philia	30,000	2.5	—	30	58	5	1.5	3	—	—	—	—	—	—
21.1.32	—	17	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	20 c.c. maternal blood	—
22.1.32	2.64	40	0.76	—	Numerous	Aniso- cytosis	18,400	0	0	49	40	6	3	2	—	—	Faint +ve	120 c.c. citratd blood	—	—
27.1.32	2.96	50	0.86	—	7,200	Poly- chromasia	18,000	2	0	31	59	4	3	1	—	—	—	—	—	Spectroscopic and chemical tests for blood in stool nega- tive
29.1.32	—	40	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
3.2.32	2.45	30	0.62	—	2,010	—	40,200	3	0	35	50	10	1	1	—	—	—	—	—	—
5.2.32	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	140 c.c.	—	—
8.2.32	3.80	58	0.76	—	1,840	—	18,400	0	0	37	59	3	1	0	—	—	—	—	—	—
16.2.32	2.10	39	0.94	—	1,600	Aniso- cytosis	16,200	1	0	17	72	9	1	0	Slight 0.51 % marked 0.45 % (saline)	—	—	—	—	—
23.2.32	—	—	—	—	—	Poly- chromasia Poikilo- cytosis	—	—	—	—	—	—	—	—	—	—	—	—	74 c.c. subcut. saline	Intermittent bleed- ing from nose. Much vomiting and fever
25.2.32	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	170 c.c. maternal blood	—	—

CHART 6. Case 18

Date.	R.B.C. in millions per c.mm.	Haemoglobin % (Haldane).	C.I.	Nucleated erythro- cytes per c.mm.	Reticulocytes per 100 R.B.C.	W.B.C. per c.mm.	Polymorphs %.	Myelocytes %.	Lymphocytes %.	Monocytes %.	Eosinophils %.	Basophils %.	Remarks.
15.8.33	3.90	86	1.10	0	5	5,250	43	0	44	11	1	1	No abnormal cells
24.8.33	4.40	86	0.97	0	8	8,400	29	0	67	2	1	1	"
25.9.33	5.12	80	0.78	0	0.6	—	30	0	78	3	0	0	"

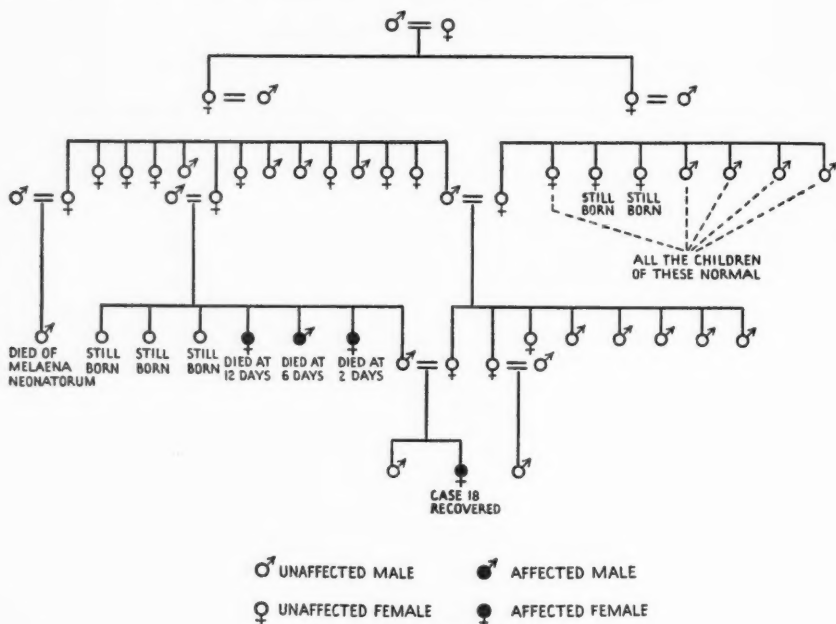
CHART 6. Case 18

26.2.32	4.22	72	0.85	—	7,800	—	26,000	2	0	61.5	32	3	1.5	0	—	—
7.3.32	3.90	60	0.77	—	Few	Aniso- cytosis	19,100	1	0	45	46	6	1	1	—	—
12.3.32	4.65	56	0.60	—	Few	Aniso- cytosis Poly- chromasia	7,800	4	2	36	49	6	2	1	—	—
29.3.32	2.66	38	0.73	—	4,284	—	30,600	4	4	34	54	4	0	0	—	—
1.4.32	2.26	35	0.70	—	4,000	—	18,000	6	2	32	56	4	0	0	—	—
5.4.32	—	—	—	—	—	—	—	—	—	—	—	—	—	150 c.c.	—	—
19.5.32	2.70	34	0.62	—	—	—	27,000	1	0	32	59	8	0	0	—	—
29.5.32	—	—	—	—	—	—	—	—	—	—	—	—	—	120 c.c.	—	—
30.5.32	2.50	42	0.84	—	6,200	Aniso- cytosis Poly- chromasia P. Baso- philia	—	1	1	51	43	3	0	1	—	Died during night

*Case 18. P.T.*

*Female.* A case of prolonged icterus neonatorum with evidence of hereditary transmission: spontaneous recovery.

*Family history.* The parents were healthy and the only other child was unaffected. A study of the family tree (Chart 7) suggests that the disease had been hereditarily transmitted as a Mendelian recessive.

CHART 7. *Case 18*

*Clinical history.* The mother's health had been good during pregnancy, and the infant was born at term, weighing 5 lb. Labour was normal and the conjunctivae were icteric at birth. By the third day she was yellow in the face and her body became fully jaundiced about 6 weeks of age, the depth of colour varying from time to time. The stools were always coloured, and the urine stained the napkins dark yellow. There had been no bruising or haemorrhage. Vomiting had occurred.

On examination in hospital at nine weeks old we saw a baby apparently healthy except for lemon-tinted skin and conjunctivae. Weight 8 lb. It was reported that the baby was already on the mend; the spleen could not be felt and the liver was not enlarged. Nervous system normal except for slight stiffness of legs. Haematological data: Chart 6.

*Pathological data* (specimens taken on admission, 9 weeks old). Van den Bergh: direct reaction negative; indirect test = 3.4 units of bilirubin. Fragility of erythrocytes: incomplete haemolysis in 0.30 per cent. NaCl (normal = complete in 0.33 per cent.). Trace of haemolysis in 0.33 per cent. NaCl (normal = trace in 0.42 per cent.). Urine acid, chlorides diminished, no abnormal constituents. Wassermann reaction of infant's and parents'

blood negative. A week later the jaundice had faded, the baby appeared well, and has remained so until past the fourth month. No treatment, except small doses of iron, was deemed necessary.

*Case 19. P.M. 52/33. 1931.*

*Female.* Congenital syphilis: prematurity; erythroblastosis.

*Clinical history.* Female infant of syphilitic parents. Born prematurely at 7/12 with a rash, and seen, when 2 weeks old, with the following signs: syphilitic pemphigus, syphilitic wig, osteoperiostitis. Icterus. Enlarged liver and spleen. Wassermann reaction of patient and its parents positive. Died at 4 weeks old of convulsions.

*Autopsy.* The findings at autopsy were those of neonatal congenital syphilis, and nothing inconsistent with that diagnosis was recorded.

*Histology. Liver:* the capillaries were engorged, and the polygonal cells showed degenerative (probably post-mortem) changes. The liver-cell columns were widely separated. The capillaries and sinusoids contained large numbers of megaloblasts, erythroblasts, and normoblasts. Bile-pigment had been deposited in the cells and bile-capillaries. The bile-ducts and portal tracts were normal, and there was no fibrosis.

*Spleen.* There was congestion and obvious haematopoiesis. Deposition of bile-pigment.

*Suprarenal.* Congestion of cortex and medulla and much haematopoiesis in the latter.

*Comment.* These histological findings are identical with those of icterus gravis neonatorum.

We are indebted to the Honorary Staff of the Hospital for Sick Children for allowing us facilities in investigating and publishing their cases, to Dr. David Nabarro as Director of the Pathological Department and to Dr. W. W. Payne as Biochemist, to Dr. A. Maitland Jones and Dr. Wilfred Pearson for allowing us to publish cases under their care at the London and University College Hospitals respectively, to Dr. J. D. Flew for material, to Mr. D. Martin and Miss U. Bailey who each gave generous assistance, to Mr. V. Cobbett for the preparation of micro-illustrations, and finally to the Medical Research Council for assisting in the expenses of the investigation.

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## DESCRIPTION OF PLATES

PLATE 12. FIG. 1. Case 1. Section of liver. Haematoxylin and eosin. Camera lucida drawing  $\times 600$ .

FIG. 2. Human foetal liver from a premature twin born after 23 weeks' gestation. There is a striking resemblance between the foetal haematopoiesis in this section and that of Fig. 1. Bile-pigment absent and cell vacuolation ~~prominent~~. Haematoxylin and eosin. Camera lucida drawing  $\times 600$ .

FIG. 3. Case 9. Section of liver. Van Gieson's stain. Camera lucida drawing  $\times 250$ .

PLATE 13. FIG. 4. Case 11. Section of liver. Mallory's stain. Camera lucida drawing  $\times 100$ .

FIG. 5. Case 2. Grey matter in the floor of the 4th ventricle. Celloidin embedding. Haematoxylin. Camera lucida drawing  $\times 500$ .

FIG. 6. Case 3. From the right parietal region near the lateral ventricle. Stained for fat by Scharlach R. and counterstained with carmine. Camera lucida drawing  $\times 75$ .

PLATE 14. FIG. 7. Case 2. The darker portions in the basal ganglia and cortical region were stained yellow.

FIG. 8. Case 2. Section of the inferior olivary body. The dark portions were stained a deep yellow. Celloidin haematoxylin preparation  $\times 10$ .

PLATE 15. FIG. 9. Case 10. Section of the spleen. Van Gieson's stain  $\times 300$ .

FIG. 10. Case 3. Section of corpus Luysii stained by Scharlach R. showing partial necrosis.  $\times 50$ . The portion enclosed by the square is reproduced in Fig. 11.

FIG. 11. Case 3. Corpus Luysii.  $\times 700$ .

FIG. 12. Case 3. Corpus Luysii.  $\times 700$ .

PLATE 16. FIG. 13. Case 3. Corpus Luysii.  $\times 700$ .

FIG. 14. Case 3. Corpus Luysii. showing intracapillary erythropoiesis  $\times 700$ .

FIG. 15. Case 3. Right corpus Luysii.  $\times 1000$ .  
*stained for fat*



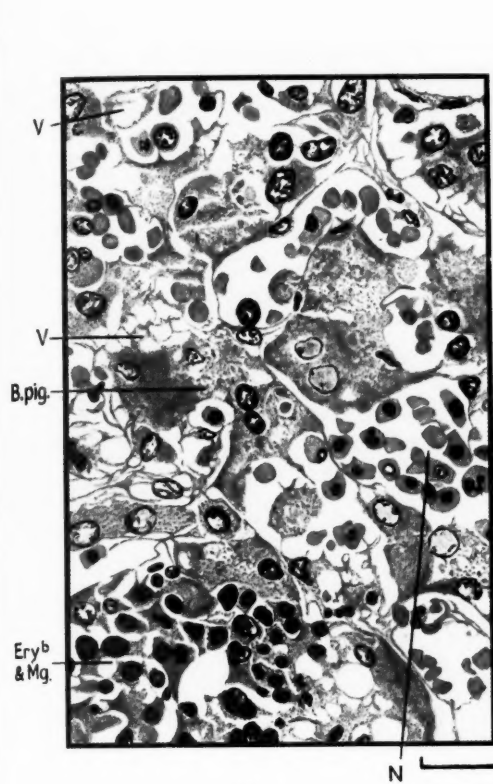


Fig. 1.

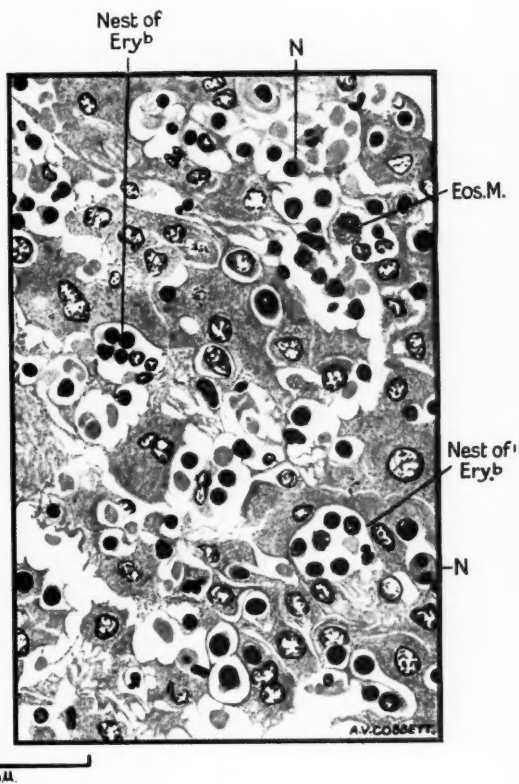


Fig. 2.

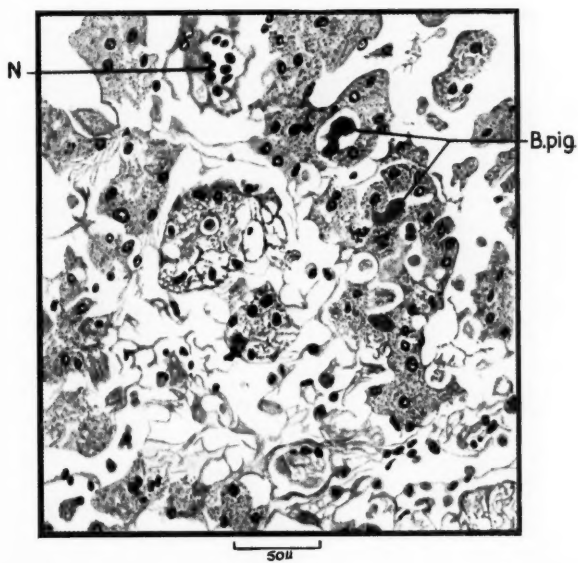


Fig. 3.



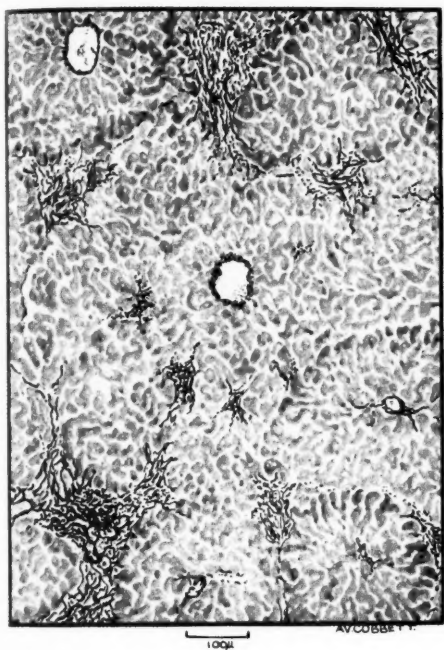


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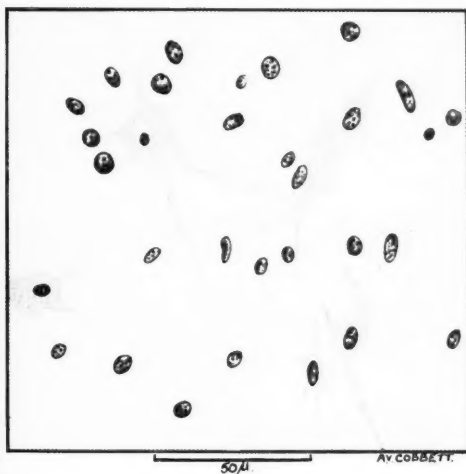


Fig. 5.

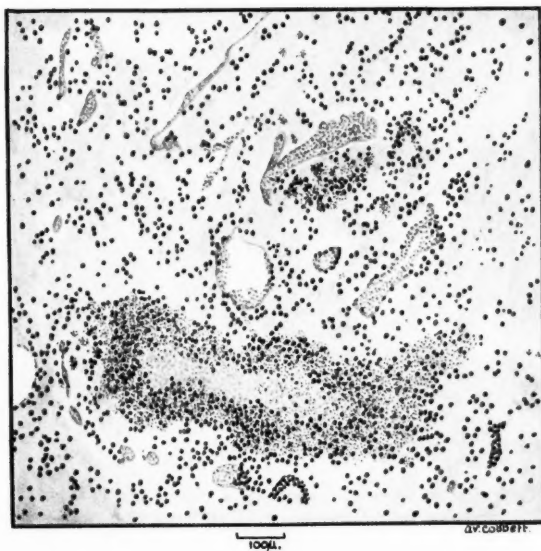


Fig. 6.



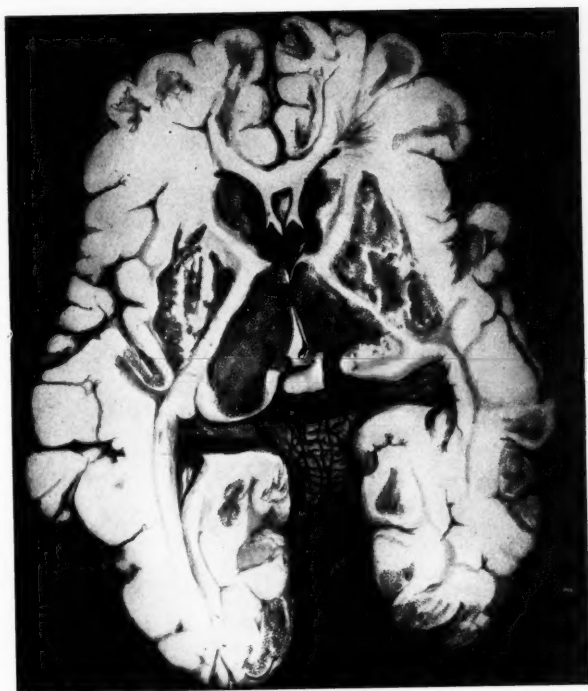


FIG. 7

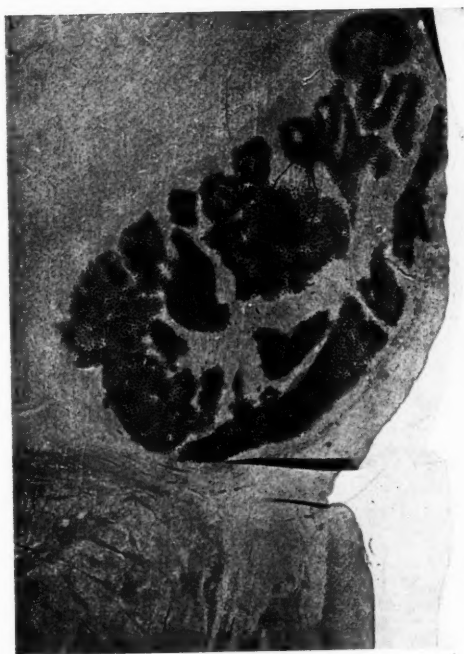


FIG. 8





FIG. 9

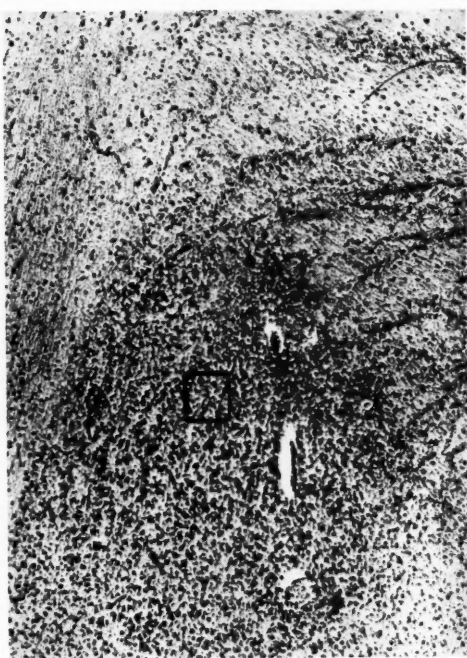


FIG. 10

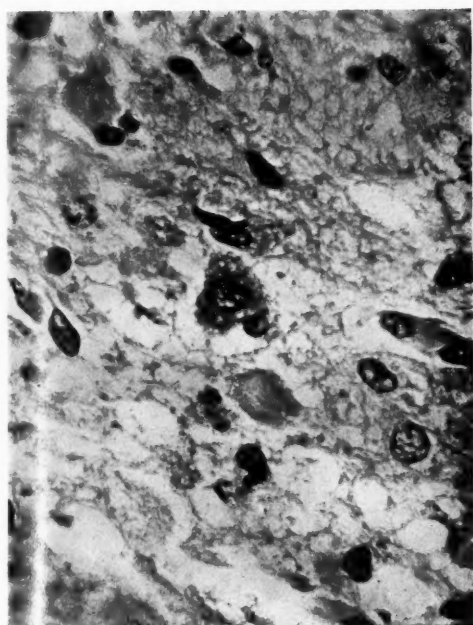


FIG. 11

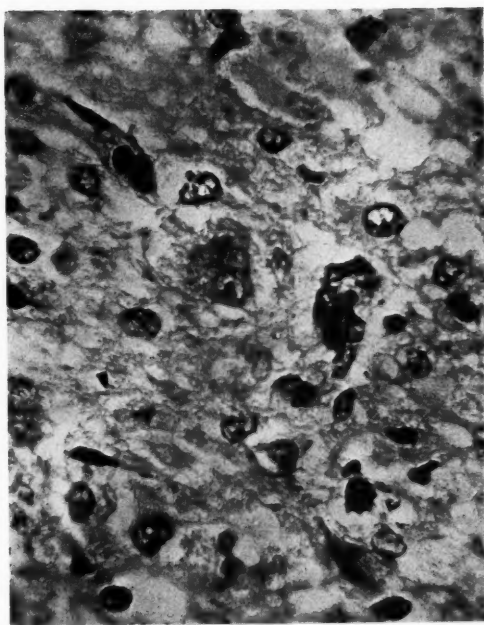


FIG. 12



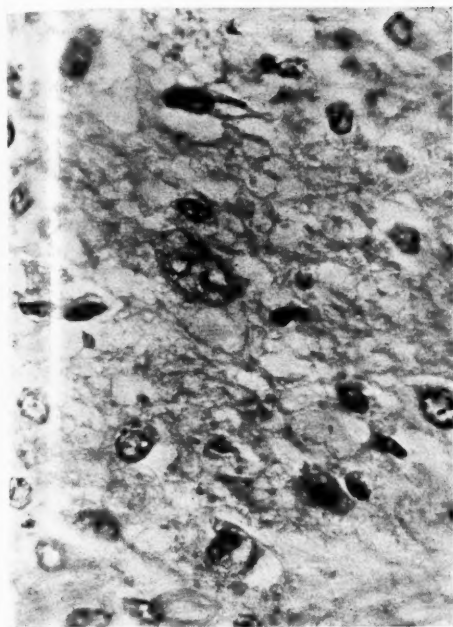


FIG. 13

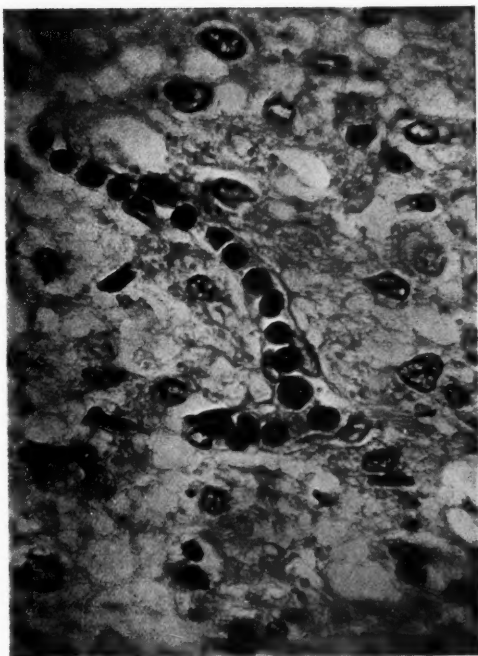


FIG. 14

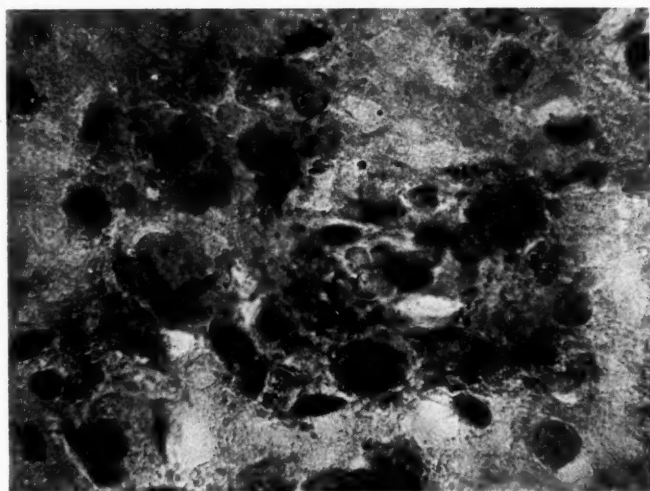
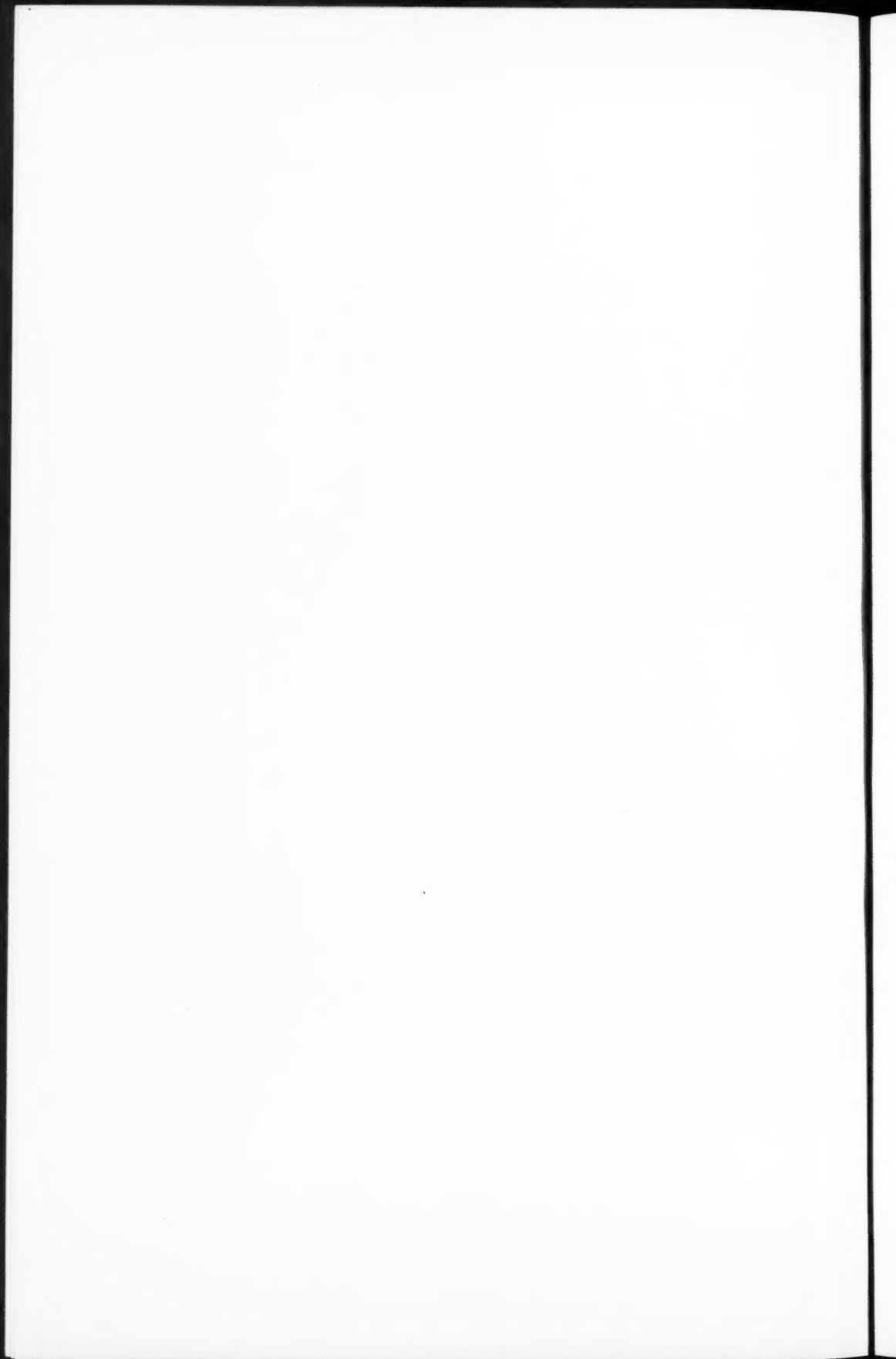


FIG. 15



PELLAGRA IN GREAT BRITAIN<sup>1</sup>

BY HUGH S. STANNUS AND CHARLES R. GIBSON

With Plate 17

PELLAGRA is certainly a rare disease in Great Britain: owing to this fact it is an affection which perhaps very few have learned to distinguish, and there can be little doubt that a proportion of the cases go unrecognized. Before 1912 there is apparently no reference to pellagra as a cause of death in this country. In that year the now classic case described by Box died and was the first entry under Pellagra in the Annual Report of the Registrar General. The publication of this case resulted in the appearance of a number of papers, seventeen in all, during the years 1913-1914 dealing with cases of pellagra. During the ensuing twenty years about an equal number of articles have appeared. The case described below is perhaps the only case recorded in this country of which a detailed history of onset, progress, and recovery is available; at the same time it is the only case which is known to have survived an observation period of two years.

In the second part of this paper will be found a summary of all the published cases in this country.

*Case History*

The following history was elicited from an intelligent mother:

Family history unimportant: the mother and father of the child are healthy. There are no other children, and there have been no miscarriages. The child was born on 25th August 1923, weighing seven pounds, at Weymouth; she was breast-fed for three months, and then till twelve months old brought up on Allenbury's food. At nine months of age she was taken to live at Poole. When twelve months old she suffered an attack of diarrhoea, 'due to teething', which lasted a week. Except for this set-back she thrived and steadily gained weight on a diet consisting of milk, bread and milk, potato and gravy, orange juice. When she was sixteen months old the family moved back to Weymouth. During Easter 1925, when twenty months old, while staying at Parkstone, she suffered from an acute conjunctivitis (bilateral) lasting three or four weeks; since then she has been 'liable to have blood-shot eyes'. She also had a mild attack of whooping-cough about this time. Fish had been added to the diet, but no meat.

<sup>1</sup> Received November 9, 1933.

In December 1925 the family moved to their present address, Weymouth. The child has always had a good home, has been well housed and well looked-after, in comfortable surroundings. The father is a working man, but steady, and all his earnings are spent on his family.

In February 1926 the child suffered an attack of pleurisy, but normal recovery took place, and in the summer of that year she was a particularly healthy child of three years of age. She was taking a full diet including eggs, some fish, but not much meat.

The first symptoms of her present illness began in April 1927 at the age of three years and eight months, when a severe 'sunburn' with blistering of the skin occurred, involving the nape of the neck, the exposed parts of the face, the backs of the hands, and the upper parts of the legs above her socks. This lasted till September when 'it all seemed to clear up'.

At the beginning of the attack the child appeared otherwise well, but in the month of August, when she started going to school, it was noticed that she was rather 'nervous'. About the same time she began to have three or four rather loose motions in the morning before going to school, sometimes with pains in the belly and vomiting, symptoms which could not be accounted for. During the winter months 1927-1928 all these symptoms disappeared.

During Easter 1928 the exposed parts of the skin again suffered 'sunburn', but on this occasion without blistering. The skin remained reddened all the summer, but cleared up again in the autumn. During the summer the child had a bad attack of measles with severe bronchitis and conjunctivitis. With the 'sunburn' there had been some return of the other symptoms—colicky pains in the abdomen and some looseness of the bowels, and she appeared nervous and afraid to go to school, but during the winter of 1928-1929 she was again well and free from symptoms and signs except that the skin of the backs of the hands remained 'rough'.

At Easter 1929, when five years and eight months old, the child suffered the third attack of 'sunburn' with a recurrence of abdominal pain and diarrhoea. In the summer of this year she had an attack of follicular tonsillitis, and in September the tonsils were removed. From about this date she became increasingly nervous, emotional, and easily frightened without apparent good cause. She was 'sharp at her lessons' and ran about normally, but appeared to be timid of other children; she began to indulge in periods of loud singing. Her mother noticed that when being dressed she was frightened of having clothing passed over her head, a fact the mother believes is associated with a fear of the anaesthetic mask at the time of the tonsillectomy. Dark rings appeared round the eyes, and as winter approached the child developed a persistent nasopharyngeal catarrh and croupy cough.

During the winter of 1929-1930 she began to show signs of tiring easily on walking or running, and complained of slight giddiness on occasions. All the affected areas of skin, instead of clearing up, remained rather rough.

In March 1930, the child then being six years and seven months old, at a time when there had been very little sun, the fourth attack of 'sunburn' occurred; this resembled previous attacks and was accompanied again by gastro-intestinal symptoms. The child was bright and 'quick at lessons, but the very thought of school gave her diarrhoea'. The same sequence of events took place this year as in previous years, and during the winter of 1930-1931 the skin is said to have been 'fairly normal'; there was some nervousness and slight giddiness at times.

In November 1930 there was some failure of appetite and loss of weight. In December it was noticed that 'she stumbled and fell for no apparent reason except that her legs were weak'. Diarrhoea, and vomiting at times, continued during this winter, and in January 1931 there were as many as five loose stools a day.

During the early part of 1931 it was also remarked that the child was depressed and that 'her character had changed'. From being a cheerful, good-tempered child of sweet disposition, she had become obstinate, rude, ill-tempered, and emotional. She was fond of saying 'damn!' to try and shock her mother. Giddy turns were much more frequent and severe, and unsteadiness so marked that she staggered when walking and fell on many occasions; 'she shuffled her feet as if something were pulling her down'.

Such was the general condition in March 1931, when at the age of seven years and seven months the fifth attack of 'sunburn' occurred. During the next two months all symptoms persisted without any amelioration and insomnia was added.

The average daily diet during the years 1928-1930 was as follows: early morning, a cup of tea and a biscuit; breakfast, a rasher of bacon and a tomato or a boiled egg, a glass of water; mid-morning at school, a slice of bread and butter, a glass of milk; mid-day dinner, two potatoes, peas, gravy, sometimes fish like mackerel, or chicken (she did not care much for fish and seldom would eat meat), a little milk pudding or stewed fruit; before tea, a slice of bread and butter; at tea-time an egg (she was very fond of eggs), two pieces of bread and butter with jam, sometimes tinned salmon, a glass of water or a cup of tea (she liked tin salmon and bread and butter); supper, a bowl of bread and milk or sometimes boiled onions and bread and butter, occasionally fish and chips. She had always had a certain amount of fruit—apples, bananas, and strawberries, but disliked oranges and other fruit. During 1931 the child was very difficult to feed and took little except three eggs a day, some milk, and bread and butter. The child had had pop-corn occasionally when quite young.

In May 1931 the child came under the care of one of us (C.R.G.), and a tentative diagnosis of pellagra was made. This was confirmed (H.S.S.) when the child was brought to London on June 1931 and admitted to the French Hospital.

On examination (B.B.) a well-grown, well-nourished child aged nearly seven years, exhibiting a typical pellagrous eruption on the hands and face associated with gastro-intestinal disturbance, signs of involvement of the nervous system, and an irregular pyrexia.

The eruption on the face is most striking, being strictly limited to exposed areas. The skin of the forehead, ears, and the sides of the face behind vertical lines drawn through the outer ends of the eyebrows, which has been covered by a fringe and side-locks, is quite normal. The affected regions of the face, cheeks, nose, upper and lower eyelids, and chin are the seat of an intense erythema with marked infiltration and some exudation with exfoliation and crusting. The general colour is a dull red, but where exfoliation is taking place the epidermis appears pigmented a greyish brown. The margins of the lips are inflamed and swollen and of an intense dark-red colour. At the angles of the mouth the muco-cutaneous junctions are white in colour due to the heaping-up of sodden epithelium. The eyelids are involved with the face, red and swollen, giving to the face a dull heavy appearance. At the external canthus of each eye there is a condition resembling that noted at the angles of the mouth.

The skin of the back of the hands, fingers, and wrists exhibits similar changes to those noted on the face, but in more marked degree, the thickening, roughening, exfoliation, and pigmentation being more noticeable, especially over the metacarpo-phalangeal and interphalangeal joints and the wrists. These changes extend on to the distal phalanges and to the margins of the palmar aspects of the hands, while about the wrists the exanthem forms a completely encircling band or bracelet. The skin of the palms of the hands is dry and thickened; there is hyperkeratosis with some desquamation, but no pigmentation. Elsewhere over the body, neck, and limbs the skin appears at first sight unaffected, but seen in a good light or on palpation, it is discovered to present a condition like a mild degree of 'goose-skin'. This is noticeable over the abdomen and hips, while on the outer surfaces of the upper arms the condition resembles more definitely a lichen spinulosus. The legs, which have been kept covered during the past six months by stockings, appear normal except that the skin over the patellae is roughened and pigmented. The same is true of the points of the elbows. The skin of the labia minora shows changes similar to those seen at the angles of the mouth. Similarly the puckered skin of the anus exhibits the same white sodden appearance.

The mucous membrane of the mouth and pharynx is of a darker red colour than normal, but there is no gingivitis. The tongue appears unaffected, there is neither coating, denudation, nor ulceration, but the patient complains that some foods hurt and burn her tongue. There is some salivation. The appetite is poor and capricious, the child's desires are uncertain, eggs only are asked for, meat is rejected.

The child complains from time to time of a colicky pain in the belly. The abdomen is very easily palpated, there is no distension, no tenderness, and nothing abnormal can be detected. The spleen and liver are not enlarged. There is no swelling of the lymphatic glands. The thoracic viscera are normal on physical examination. There are no urinary symptoms.

Examination of the nervous system reveals a child with a dull, almost somnolent, apathetic, and at the same time unhappy expression, partly due to the heavy drooping inflamed upper eyelids. She is highly emotional, weeping for little reason or alternatively breaking out into an unnatural peal of laughter. In contrast with her facial expression, however, she replies to questions very quickly and accurately, she is alert and her memory is good. No attempt at any psychological investigation has been made. There is no evidence of obsessions, delusions, or hallucinations.

The most characteristic objective symptom, apart from the skin condition, is a general tremulousness. It is only apparent when attempts at movement are made or when attempting to maintain some posture without support. The condition is best described as one of tremulousness rather than as tremor; the movements have nothing in common with those of chorea or athetosis, there is no intention tremor and no true inco-ordination. The muscles of the trunk, head, and limbs are alike affected as also are the muscles of the eyeballs, so that a kind of lateral nystagmus can be elicited. When the child sits up in bed, the back is rounded and the head falls forward unless supported by the arms; unless asked to remain sitting she soon sinks back into the bed as if very weary. She is just able to maintain an erect posture for a very short time, but unable to walk unsupported. The gait is very unsteady, the legs are moved very tremulously, giving the idea of spasticity, the feet are kept rather widely apart, and after a few moments

she 'crumples-up' and sinks to the ground. There is no true Rombergism or ataxia.

The apparent muscular weakness would seem to be due to loss of tonus, as the actual muscular power in the face, neck, trunk, and limb muscles, when tested in the ordinary way, is excellent.

All the superficial and deep reflexes are increased except the plantar reflexes which, though flexor in type, are difficult to elicit. The pupillary reflexes are normal, the fundi oculorum healthy, hearing unaffected.

The child complains that the erythematous areas of skin give rise to a burning sensation; otherwise subjective sensibility appears normal or but slightly diminished, and no more than might be due to the mental apathy. No astereognosis.

Laboratory examinations were carried out by Dr. Schwabacher. Blood: red cells 4,440,000; haemoglobin 90 per cent.; colour index 1.0; halometer reading 4.5; no abnormal forms of erythrocytes noted.

White cells 6,800; differential count—70.4 per cent. polynuclears (segmented forms 56.0, band forms 14.0, young forms 0), Arneeth index a slight shift to the left; 18.4 per cent. lymphocytes; 7.2 per cent. large mononuclears; 3.2 per cent. eosinophils; 0.8 per cent. basophils.

Sedimentation test (Katz formula) within normal limits.

Blood calcium normal at 10.8 mg. per cent.; phosphates a high normal at 5 mg. per cent. Examination by test meal was not done. One attempt was made but failed, and it was considered inexpedient to repeat it.

Urine: specific gravity 1.031; acid, no albumin, no sugar, a trace of acetone and urobilinogen present; phosphates 1 gm. per litre (normal 2 gm.), chlorides 4.5 gm. per litre (normal 8–10 gm.); deposit contains amorphous urates, no casts.

Faeces: a stool, passed the day after admission, was formed, pale in colour and offensive. It contained no blood, no abnormal amount of mucus or undigested starch. There were present a few partly digested muscle-fibres and soap plaques and neutral fat globules in large quantity, but fatty acid crystals were diminished. Stained smears showed a large number of gram-negative organisms, mainly bacilli, and small numbers of gram-positive sporing bacilli, diphtheroids and enterococci. Culture on McConkey plates yielded a pure growth of *B. coli*, no non-lactose fermenters and no streptococci present. In broth an actively motile non-sporing gram-negative bacillus was recovered producing acid and gas with lactose, maltose, glucose, and salicin, clot and acid with litmus milk, and indole with peptone water.

A stained smear from the vulva showed epithelial cells and leucocytes, no pus cells, together with masses of gram-negative diplococci resembling somewhat, but smaller than, gonococci and a few diphtheroid organisms. Using agar, glycerine-agar, and nutrient-agar growth of *M. catarrhalis* and enterococci obtained.

Progress of case. During the first week there was little change, the irregular pyrexia 99° to 100° F. continued, pulse 100 to 120 per minute, abdominal discomfort was complained of, but there was only a single action of the bowels each day. The rash on the face and hands began to clear up under an ointment of vaseline and lanoline.

During the second week, while it was noted that the skin condition still further improved, the general condition was worse, the temperature was higher, and the pulse more rapid. There were usually two actions of the bowels each day, and the stool was unformed or liquid, of a yellow, though

sometimes of a very dark, colour. The child could no longer sit up in bed, she lay apathetic as in a severe toxic state. There was incontinence of urine and faeces, which caused an eruption on the buttocks. The tongue was now coated with fur. There was great difficulty in getting the patient to take any nourishment; what was taken was often vomited. A differential white count showed polynuclears 53.2; lymphocytes 35.6; large mononuclears 7.2; eosinophils 3.2; basophils 0.8 per cent. Blood culture was negative. The urine showed no excess of indican. It was noticed that a stool passed on 17th June 1931 turned from a light yellow to a dark brown. Examination of this stool and a specimen of urine for porphyrin was kindly undertaken by the Wellcome Bureau of Scientific Research. The stool gave a slight positive reaction for porphyrin on spectroscopic examination, but the bands were not identical with those of haematoporphyrin and were due probably to the presence of traces of porphyrin of vegetable origin. The urine showed no evidence of the presence of porphyrin on spectroscopic examination, and it failed to photosensitize white mice (Dr. Marshall Findlay). The blood-serum was also negative for haematoporphyrin.

On the last day of the second week of observation the temperature rose to 103° F., pulse to 140, the child looked very ill, she was extremely tremulous on attempting to move the arms, and laid for the most part in a semi-typhoid state. On one or two occasions when she was being sponged the Sister noticed a sudden retraction of the head with stiffening of the neck and some arching of the back. Only a single stool was passed that day, but colicky pains were complained of; there was some vomiting and the tongue was thickly coated. A full dose of castor oil was administered, followed by a good result, the temperature reached normal, and the pulse fell to 100.

Two days later, that is two and a half weeks after admission (20th June 1931), treatment with yeast was begun—one tablespoonful of dry fresh brewers' yeast was given twice daily in milk and water. Extract of liver (B.D.H.) in drachm doses, in soup, was also administered, but discontinued after a few days.

By the end of the third week the child showed signs of improvement, the looseness of the stools and vomiting had ceased, the tongue had cleaned and the buccal mucous membrane was normal, the temperature only reached 99° F. in the evening, and the pulse was below 100 per minute for the first time since admission. She was, however, still incontinent, and saliva dribbled from her mouth. She was found to have lost five pounds in weight and was very weak and tremulous, though she said she felt better and certainly looked brighter. Nystagmus still present; the patient at times showed a return of euphoria. The skin eruption on the face had practically cleared up, leaving a brown pigmentation on the upper lids, infra-ciliary regions, nasion and the bridge of the nose with an unaffected area between the two latter areas.

The hands were still rough and presented a wrinkled, scaly, pigmented appearance on their dorsal surfaces, most marked over the joints. The palms of the hands were desquamating. The white sodden condition at the angles of the mouth had nearly gone, and that about the nymphae had disappeared.

The fourth week witnessed continued improvement, generally the child appeared brighter though sometimes unnaturally euphoric. Temperature and pulse lower, one formed stool a day, no pain, no incontinence; she was less shaky.

Very rapid progress marked the fifth week. The temperature remained

normal, bowels regular, stool healthy, no abdominal symptoms, tongue clean, appetite returned.

The child began to take a good mixed diet and gained two pounds in weight. Mentally she appeared almost normal; she sat up in bed playing with her dolls, and could walk once more, unsupported, the unsteadiness and tremulousness being much less than on admission. Muscular power excellent, but reflexes remained increased and nystagmus persisted. A blood count showed red cells 4,216,000; haemoglobin 85 per cent.; colour index 1.0; white cells 8,680; polynuclears 69; lymphocytes 20; mononuclears 10; eosinophils 1 per cent.

During the sixth week there was a further gain of three pounds in weight and general improvement all round; she was able to feed herself again and walk a few steps more, though still afraid of falling.

On 17th July 1931, during the seventh week, the patient was excited at the advent of her mother on a visit from the country to London to see her. In the evening she vomited, the temperature rose to 104° F. and the pulse to 140. She had a bad night, and during the ensuing days was far from well. The facies was dull and heavy, she was very weak and very tremulous again, she could not sit up in bed. The tongue was coated, she vomited, but the stools were normal, and there was no return of abdominal pain or incontinence. This 'attack' passed off in a few days, and there was a rapid return to her previously much improved condition.

Improvement continued in all directions during the remainder of her stay in hospital. On 31st July 1931 she was allowed to go home to Weymouth; the child's mother was instructed regarding a well-balanced diet. Yeast was administered during the whole time the child was in hospital, and has been continued since. The child was taking a good full mixed diet.

The only other observations made upon the case were in regard to photosensitiveness. On 23rd June, i.e. at a time when the rash was markedly retrogressive and three days after commencing to take yeast—an area of skin on the leg free from rash was exposed to direct bright sunshine for twenty minutes, and on 4th July for sixty minutes. No erythema appeared in the case of the patient nor in a control. During the last week in June and first week in July exposures to a carbon arc were made for 3, 6, 10, 15, 20, 25, and 30 minutes to separate areas of skin on the limbs, skin which had never been the site of a pellagrous erythema in the past. With the shorter exposures there was no reaction; the twenty-minute exposure produced a faint, the twenty-five-minute a mild, and the thirty-minute a well-marked erythema. The responses in control children were identical.

A fifty-minute exposure, using a plate-glass screen, produced no reaction.

From the date of discharge the mother has kept a diary of the child's progress, that is from 31st July 1931 to 31st October 1933. From that diary the following after-history has been extracted; at the same time the patient's dietary and treatment has been kept under supervision.

September 1931: child 'on the move all day long'; soon tires if she attempts to take a little walk in the street; interest in books and toys intermittent; memory good, but tends to run from one thing to another. The appetite is good, but she occasionally regurgitates a little food when half-way through a meal. Though there is some difficulty in getting off, she sleeps well nine to ten hours. She is better and steadier in the morning; later in the day she tends to 'stumble' more. She still has the habit of saying things a number of times over.

October 1931 : is walking better and never seems tired now, but the limbs seem stiff and she sometimes holds on to things as if unsteady. Takes nourishment well, but vomits sometimes when she eats meat. Weight  $3\frac{1}{2}$  stone.

November 1931 : at the beginning of the month not so well as the result of a 'cold'. Her speech is rather slow, she is still emotional, she is not very clever with her fingers, as in picking up a coin off the floor. At the end of the month she was better and her walking had improved ; she looked 'the picture of health'. She has continued on yeast and taken Livogen and now Radiostoleum.

December 1931 : walks a quarter of a mile, tries to write but has difficulty in holding her pen, the limbs still seem 'stiff', appears rather 'nervous' and will not stay in a room alone. Bowels as a rule regular and stool normal, there is occasionally some upset which is always corrected by a dose of castor oil.

January 1932 : there is general improvement all round. She is able to use a pencil, she can spin a top, and manages three or four rounds with a skipping-rope ; still emotional and easily moved to tears or laughter. Weight 3 stone,  $9\frac{1}{2}$  pounds.

By the end of February 1932 the gait is said to be normal. She walks half a mile and plays with other children. She has again become the shy child rather than the excitable, talkative, noisy little person she was when ill. She is writing and knitting and trying to paint and do sums.

March 1932 : now joining other children in their games ; manages ten to fifteen turns with a skipping-rope ; is sometimes a little irritable and nervy, but will now remain in a room by herself.

April 1932 : no progress this month. She had to have some teeth out and was scared by the gas-mask. She is, however, eating well and tolerates a good mixed diet. It is of interest to note that during the first week in the month 'the face and hands looked as if they had been touched by the wind' ; dark rings again appeared round the eyes. These signs soon passed off, but recurred in the middle of the month, the skin of the face being affected 'where the gas-mask had touched her face'. Towards the end of the month there was some abdominal pain and mild diarrhoea which cleared up after a dose of castor oil. Her temper was a little uncertain.

During May there was again no progress, but no erythema appeared as in previous years, though 'the skin of the hands is showing up a bit rough and looks dirty'. Movements are rather slow, she appears to be stiff at the hips, knees, and ankles, and she stoops. Bowels sometimes loose. Weight 3 stone,  $10\frac{1}{2}$  pounds.

In June improvement again set in. The appearance of good health is restored and the child is much stronger, she can walk one and a half miles ; she varies a good deal, one day she will hold her own with other children, another day she fails and becomes emotional. There was only one attack of diarrhoea during the month. Her bare arms and legs have shown no reaction to sunlight.

In July she learned to ride a bicycle. Physically she shows marked but slow improvement. She is now able to use her hands quite well.

Improvement continued throughout August. Mentally and physically she is better ; she is still a little frightened of the noise and traffic in the street. The skin of the hands is now no longer rough and her face looks normal, though if overtired she gets rings round the eyes.

In September 1932 the child was brought to London to be seen. On

casual examination the skin might be passed as normal, but closer scrutiny reveals the skin on the backs of the hands to be in places rather dry and shiny, and over the knuckles to be finely rugose and pigmented, the characteristic brownish lilac colour extending on to the distal phalanges of the fingers. The face, too, would pass for normal, but on making the child cry a flush develops over those areas which were previously the seat of the erythema; this has been noticed by the mother to occur on a hot day, and is of course due to the permanent telangiectatic changes in the skin following the pellagrous eruption. The skin of the forearms and legs has remained clear. The lips, tongue, buccal mucous membrane appear normal. The child is obviously still rather easily upset and emotional; on weeping the pupils dilate widely. The knee-jerks are still increased and clonic in response. Muscular power very good, no inco-ordination, no tremor, no Rombergism. She is not very steady on her feet, as if slightly spastic, and may topple over if gently pushed.

By the end of the year 1932 further progress is noted by the mother. 'Her nerves are better', things do not scare her, she is more nimble on her feet, and can walk several miles. She sits and stands on a swing in motion, and has taken to roller skates on her own accord.

She appears quite quick at Sunday school, and her needlework has improved. She has a good appetite, and at Christmas ate of everything without any upset.

During the spring of 1933 the mother reported that the child had made great strides. She is well and has a hearty appetite, she eats anything. She is steady on her legs and her speech is normal.

She is no longer frightened of traffic and is contented; she sleeps well. At times she has appeared rather impulsive, and sometimes she would seem to be day-dreaming, but these things are becoming less frequent. Her memory is excellent.

On 29th June 1933 the child was again brought to London to be seen, when nearly ten years old, six years since the beginning of her illness and two years since her admission to hospital. The child is apparently in excellent health. During the sunny weather she has been running about out of doors all day, hatless and without stockings; she bathes in the sea every day and goes for five-mile walks. She runs, hops, cycles, and skates. She goes off into the country-side with other children happily, but is occasionally apparently frightened of something. Speech is normal and she reads interestedly, but she has not yet gone back to school, and 'will not yet settle down to learn lessons or write properly'. She eats anything and everything, the bowels are regular and the stools normal, there is never any vomiting.

The lips, mouth, and tongue are normal; the conjunctivae are no longer injected. The skin of the back, chest, and limbs is browned normally by exposure to the sun. There has been no return of the 'sunburn' this year. The exposed parts of the face appear more healthy, the dull red colour which persisted so long is much less. The slight roughness of the backs of the hands has persisted since 1931, and the skin over the interphalangeal joints is slightly pachydermatous and pigmented as before; the distal phalanges have also remained pigmented. The outer surfaces of the upper arms still exhibit a kind of goose-skin roughness, and the skin over the lower part of the shins is a little shiny and scaly.

Muscular power very good, no inco-ordination, no Rombergism. The child will carry a cup of tea upstairs; there is no tremor, but the gait appears still

slightly spastic and there is just a slight unsteadiness when she attempts to turn round quickly. All reflexes still increased.

During the autumn of 1933 the child went to school three hours a day; 'her teacher is very pleased with the way she is getting on'.

She is still unsteady but it is less marked, otherwise her condition is as described in June.

#### *Geographical Distribution of Pellagra*

It would be difficult to give, with any degree of precision, facts in regard to the distribution of pellagra throughout the world, without, on the one hand, writing a complete history of the disease from the time of its first recognition in Spain two centuries ago and, on the other hand, without being in possession of much more complete observations than are at present available.

Casal's original observations were made among the peasant population near Oviedo in the province of the Asturias in 1735, but they were not published till after his death—*Historia natural y médica de el principado de Asturias, obre posthuma del doctor D. Gaspar Casal, medico de su Majestad. Madrid 1762*. Casal's writings were, however, made known before that date by Thiéry, a physician in the suite of the Duc de Duras, Louis XV's Ambassador to Spain, who had met Casal in Madrid and made textual copies of his notes concerning *mal de la rosa*, which he sent to Chomel, doyen of the Faculty in Paris, where they were read before a meeting in 1755, to appear later in an article entitled 'Lepra asturiensis' in Sauvage's *Nosologie méthodique*.

The disease was subsequently notified in a number of provinces adjoining the Asturias, but very little information concerning pellagra in Spain has been published since. The number of cases is said to have greatly diminished after the year 1910, but it would appear that cases still may be found among the poorer inhabitants of the areas originally affected.

The second milestone in the history of pellagra was the recognition of the affection under the designation *scorbuto alpino* among the inhabitants of the villages in the neighbourhood of Feltre, about 1755, by Antonio Pujati, a distinguished Venetian physician. Later, evidence was adduced to show that the disease had been well known to medical men practising among the poor agricultural populations of other areas, possibly as far back as 1720, in the Ligurian mountains. The identity of the affection as known in the Venetian states with that seen in the provinces of Lombardy remained long unrecognized, and it was Fanzago in 1815 who eventually gave conclusive proof upon the point.

The ravages of pellagra throughout practically the whole of northern Italy are well known. The 1830 census revealed that in many areas 5 per cent. of the population were suffering from pellagra. In 1881 among the inhabitants of eight provinces, numbering sixteen and a half millions, there were one hundred thousand cases of the disease.

It is now generally stated of Italy that pellagra has ceased to exist as an endemic disease since 1914, and it is very difficult to obtain any further information at the present time.

The history of pellagra in Spain and Italy was repeated in France. In 1829 a country practitioner named Gustave Hameau read a paper at Bordeaux in which he described 'Une maladie de la peau que je crois peu connue et qui est des plus graves, menace d'attaquer la population du que j'habite'. This affection he had noted since 1818 among the miserable inhabitants living just to the south of the bay of Arcachon, in the Teste-du-Buch district. It, however, seems probable that the disease was widespread some years before, then known as *la gale de Sainte-Aignan*. Further investigations showed that the disease had an even wider distribution. In 1843 it was estimated that there were 3,000 pellagrins in the Landes, and that the disease was endemic throughout the whole of meridional and occidental France. Billod pointed out (1865), moreover, that sporadic cases were occurring in the north, and that the affection could be found in practically every asylum in the country. Since 1880 the disease is said to have practically disappeared, but isolated cases or small groups of cases do occur much as in our own country.

Pellagra was recognized in the Balkan states, the valley of the Danube, Greece, Poland, and South Russia during the first half of the last century, in Serbia about 1810, in Bukovina and Wallachia in 1855. In 1856 nearly 3.0 per cent. of the population of Gorizia were pellagrins and 3.2 per mille in Corfu. In 1898 it was estimated that there were twenty-one thousand cases of pellagra among 5,300,000 inhabitants of Moldo-Wallachia. In Roumania in 1882 it was calculated that 4,500 of the total population of just over five million were suffering from the disease.

Serbia and southern Russia have during recent years suffered a very heavy visitation, comparable to that in Italy long ago.

The Near East also furnishes examples of minor endemics, including Turkey, Armenia, Persia.

The disease is known in Portugal, and recently attention has been drawn to the fact that cases of pellagra are not uncommon in the mental institutions in Denmark.

Germany, Holland, and Belgium appear to have escaped any big endemic, but sporadic cases have been reported.

During the present century pellagra has become an economic problem of very considerable importance in the United States.

To Dr. Gray in New York and Dr. Tyler in Massachusetts in 1863 is usually given the credit of the first recognized cases of the disease. A few sporadic cases appear to have been noted in the eighties. Dr. Nile saw his first cases in 1900. In 1902 a case was reported by Dr. Harris, and in 1907 others were discovered in the mental asylums of South Carolina and Alabama and in Charleston in 1908, followed in quick succession by many from a number of states.

In 1910 it was stated that a total of 1,000 pellagrins had been notified from thirteen states. By 1916 some 40,000 cases were known.

The disease is endemic in every state, with a heaviest incidence in the cotton belt and the Mississippi valley, where in 1931 it was estimated there were 50,000 cases.

The first case of pellagra in Canada was noted in Ontario in 1914. During the ten years ending 1922, thirty deaths from pellagra were notified to the Registrar-General.

Pellagra has been described in the West Indies—Jamaica, Barbadoes, St. Lucia, Haiti, from Mexico, the Panama zone, Guiana, Brazil, Uruguay, and Argentina, but little is known of the true incidence of the disease in these countries.

The disease, as is well known, is endemic in North Africa, possibly over a wide area of the northern part of that continent. The first description of pellagra in Egypt occurs in an article upon *Leproses* by Pruner Bey, 1847. Abeille reported the disease among Arabs in Tunisia in 1851. It was Sandwith, however, who showed in 1892 how widespread the affection really was among the agricultural population of the Nile delta, where it has remained as an endemic ever since.

During the South African War, Sandwith diagnosed pellagra in two inmates of Robbin Island Asylum, Cape Colony. Except for these two cases pellagra was unknown in Africa south of Egypt until 1910 when Stannus recognized as pellagra an outbreak of disease in the Central Gaol, British Central Africa. Pellagra was subsequently noted in North-east Rhodesia, and groups of cases were recognized in the Cape Province, Natal, Transkei, in Pretoria, Durban, in Basutoland and the Tugela valley, later still in some of our West and East African colonies.

In the majority of instances the disease has occurred in small institutional groups, as in prisons, &c.

The same is true of India, China, Central Asia, where outbreaks have occurred in leper colonies. Sporadic cases have also been reported from these countries and from Malay, Straits Settlements, Shanghai, Singapore, Siam, Ceylon, Surinam, Korea, and the Philippine Islands.

Sporadic cases occurring in Australia have also been recorded.

There is no doubt that this brief sketch concerning the distribution of pellagra gives but little idea of the truth. Pellagra is a disease with which but comparatively few are familiar; it is a disease which may easily escape notice, especially in native territories, and even when under observation pass unrecognized.

Observations are published from time to time from various parts of the world upon some symptom complex, in some groups of individuals, which is obviously due to pellagra without the writer recognizing it, just as in this country cases are seen from time to time and go undiagnosed.

## PART II

## A. SUMMARY OF ALL THE PUBLISHED CASES IN THIS COUNTRY

On analysing the cases up to date, with the exception of a few which were not followed up and their subsequent history remains unknown, all, with a single exception, ended fatally. The earlier cases were apparently not returned as dying of pellagra, and as above stated no deaths from pellagra appear in the Annual Reports of the Registrar-General before the year 1912.

The actual figures for the period 1912-1931 are as follows:

	1912	1913	1914	1915	1916	1917	1918	1919	1920	1921	1922	1923	1924	1925	1926	1927	1928	1929	1930	1931	Total.
Male	1	1	1	3	3	0	0	0	0	0	2	4	2	0	0	1	1	0	1	0	20
Female	0	9	2	13	7	9	1	0	2	4	12	9	7	9	6	7	4	1	5	4	111
	1	10	3	16	10	9	1	0	2	4	14	13	9	9	6	8	5	1	6	4	131

The case in 1912 was Box's case; in the figures for subsequent years are included a certain number of sporadic cases, but the majority of cases are from among the inmates of our asylums. With the exception of these groups of asylum cases, the disease has never appeared as an endemic in this country as has occurred in Spain, Italy, and France in years gone by, in the United States in more recent years, or as it is seen in Roumania at the present time. No attempt will here be made to deal with the aetiology of the disease, but the greater incidence in the female sex will be noticed and the association with mental disease will be remarked. In the United States an attempt has been made to distinguish a group of cases associated with alcoholism under the designation 'alcoholic pseudopellagra'; also to define a second group, when the affection is associated with some organic disease of the gastro-intestinal tract, as 'secondary pellagra'. Further, on the Continent some observers would assign to a separate group under the term 'pellagroïde' all those cases exhibiting the pellagrous eruption unassociated with other symptoms. There is, however, no valid reason for such an attempt at differentiation; they are all cases of pellagra. They are, however, particularly interesting when studying the pathogenesis of the disease. It is worthy of note that no cases of alcoholic or secondary pellagra have been recorded in this country.

The clinical picture in pellagra may vary considerably and the grouping of cases into certain types may serve a useful purpose, so long as it is remembered that experience of large numbers of cases will show that all intermediate forms may be met with.

*Cases 1-2.* The first mention of pellagra in Great Britain occurs in Billod's 'Traité de la Pellagre', 1865 (1). On page 101 he says:

'M. le docteur Brown, inspecteur-général du service des aliénés de l'Écosse,

m'écrivait le 14 décembre, 1860 que, pendant une inspection dans les parties les plus reculées de l'île et vers l'Orient, il avait observé chez deux idiots de la même famille une alteration de la peau qu'il qualifie d'une espèce de pellagre, ajoutant qu'il n'a jamais vu d'autres exemples de la pellagre italienne.'

Apart from any other details it is uncertain whether this statement by Dr. Brown should be taken at its face value.

*Case 3.* The first case to be reported in our own literature was that of a woman thirty-three years of age, a spinner of Arbroath, under the care of Howden (2) in 1866 in the Montrose Asylum.

She was admitted with mental depression in the early part of the year, her symptoms becoming worse in May and June when a typical erythema appeared on the face, hands, and knuckles, associated with the onset of diarrhoea. On a number of occasions she became excited and sleepless and was suicidal; weakness marked and she was unable to stand. In October she began to improve and by January she had recovered.

The after-history of this case is not mentioned, the probability is that she relapsed the following spring.

*Case 4.* In 1906, that is after a period of forty years during which time no cases were recorded, which means probably that no cases of the disease were recognized as such, Brown (3) reported what he claimed to be the first case of pellagra to be diagnosed in England.

The patient, a twenty-one year old girl, seen at Rockferry in Cheshire, after twelve months ill health with obstinate constipation, headache, lassitude, depression, and severe pains and hyperaesthesia in the trunk and limbs, suddenly developed an acute febrile attack lasting three weeks. The pharynx was congested and ulcers appeared on the palate and tonsils with marked salivation; there was diarrhoea with the passage of twelve pea-soup stools per diem; a slight papular rash was noted about the outer aspect of the right knee, ankle, leg, and on the abdomen. At the end of the third week all the symptoms abated and she completely recovered.

It seems more than probable that the diagnosis was an incorrect one in this case, the more so as it is obvious that the doctor was influenced in calling the case pellagra by the history which was elicited, of the girl having eaten daily a handful of poultry-food containing maize.

*Case 5.* In 1909 Brown and Low (4) published their case—a girl of twenty-one years of age admitted to the Royal Asylum, Edinburgh, in July 1908, from Shetland.

On admission she was depressed, later agitated and emotional. This was followed by a period of excitement with loud talking, singing, and laughing and delusions of being poisoned. There was tremor of the upper limbs and weakness with spasticity of the legs and increased knee-jerks; she was unable to stand or walk. A typical erythema appeared upon the face, neck, hands, fingers, and forearms, though unexposed to the sun's rays; vaginitis, stomatitis, and intermittent diarrhoea completed the picture of a case which resulted in death. The previous history showed that during the summer

months of 1905-07 she had been employed salting fish and had lived on bread and tea, while during the rest of each year she had lived at home enjoying a plentiful and varied diet, containing some rice and oatmeal but no maize.

*Cases 6-11.* In 1912 the results of investigations made in Scotland in connexion with Sambon's Simulium Theory of transmission of pellagra were published by Sambon and Chalmers (5). They make mention of six cases in which the history was suggestive of pellagra.

(a) A married woman, aged forty, who had died in 1911 with symptoms of pellagra, under the care of Drs. Bryson and Cranston Low.

(b) Her sister who was considered to be a possible case.

(c) and (d) A woman and child at a farm near Colinsburgh who exhibited an erythema of the hands and forearms.

(e) A man from Uist, a case of dementia admitted to Montrose Asylum in 1881, who was said by an attendant to have had attacks of diarrhoea and salivation, and an eruption on the backs of the hands in the spring.

(f) A man already deceased, an inmate of the Aberdeen Royal Asylum, in whose case there was a history of chronic dementia associated with an erythematous eruption on the face and hands.

Sambon had a wide clinical knowledge of pellagra, and these cases with their suggestive histories almost certainly point to the sporadic occurrence of the disease in Scotland.

*Cases 12-13.* The next two cases to be recorded (July 1913) were the two boys, brothers, observed by Box (6) in St. Thomas's Hospital in 1910 and 1912 respectively.

The first lad died in 1910, aged eleven, after discharge from hospital, and a diagnosis of pellagra was only made in retrospect when his brother, aged eight, came under observation in hospital and there died in 1919. This second child has become quite an historical case, the clinical picture was very fully described by Box and the histopathological findings by Mott. Clinically the case resembled very closely that described by the authors (1933).

*Cases 14-15.* In July 1913 Sambon (7), published two further cases.

(a) A man aged thirty-six, of Beaulieu, Hants, complaining of headache, dizziness, weakness, and diarrhoea, with tremor of the hands and exaggerated knee-jerks, associated with a symmetrical erythematous dermatitis involving the face, neck, dorsa of the hands and feet and scrotum which had recurred for three years.

(b) A boy aged seven, a brother of Box's cases. This boy presented a typical mild pellagrous erythema on the face, the backs of the hands, and the wrists. The knee-jerks were increased, but there were no other symptoms. The three brothers were the children of well-to-do people and were said to have always had a good mixed diet; one had been fond of pop-corn, but the youngest certainly had not had maize. What happened to the third child is not known.

Following upon the publication of Box's cases a whole series of cases, which otherwise possibly would have remained unrecognized, was recorded.

*Case 16.* A fatal case is recorded by Hammond (8) in the same year (1913).

A lady aged thirty-three began in the spring of 1911 to suffer with lassitude, loss of appetite, coated tongue, constipation, abdominal pain and tenderness, headache, and an evening temperature of 99.7° F. Appendicectomy was followed by temporary improvement, later symptoms of ulcerative colitis (*sic*) supervened which improved somewhat under treatment. Late in the spring of 1912, after exposure to sunlight in her garden, a dermatitis of the hands and wrists manifested itself, followed by affection of the cheeks and lips, with the formation of bullae and suppuration. Towards the end of 1912 the general condition was worse, and jerky movements of the head with spasms which spread from the shoulders over the whole body developed; the knee-jerks were exaggerated. An unnatural mental activity showed itself and she had strange appetites. In April 1913 she died with marked prostration and cachexia.

*Cases 17-18.* Later in July 1913 Sambon (9) placed on record two other cases referred to him.

(a) A girl aged seven, living at Bridgnorth, Shropshire. For three years she had had 'eczema' each spring, affecting the hands, forearms, and face; for something over two years she had been liable to 'seizures', she would call out that she felt giddy, have a slight convulsive attack with twitching of the left arm and leg, then fall to the ground with no loss of consciousness. The child was dull, speech was indistinct, hands tremulous, knee-jerks increased, Rombergism and a dorsal plantar response in the right foot also noted. Diarrhoea occurred in attacks. The child died in a fit.

(b) A woman aged sixty-eight, living in Cardiganshire. For twenty years she is reported to have had a recurrent dark-red erythema on the backs of the hands, the bridge of the nose, and upper lip, but no nervous or other symptoms.

*Cases 19-21.* In August 1913 Sambon (10) reported still further cases which had been brought to his notice.

(a) A girl aged seventeen, under the care of Dr. Stephenson at Prestwich County Asylum. She was dull and stupid, she had choreiform movements of the arms, a spastic ataxic gait and increased knee-jerks, associated with diarrhoea and a recurring typical dermatitis.

(b) A woman forty-five years of age, admitted to King's College Hospital. In this case the diagnosis must remain uncertain.

(c) A second case at Prestwich Asylum.

*Cases 22-24.* At the Middlesex County Asylum, Napsbury, Blandy (11) then recognized three cases in women inmates aged twenty-nine, forty-six, and thirty-seven, suffering respectively from confusion with excitement, agitated melancholia, and stuporose melancholia. All showed the typical rash and two suffered with diarrhoea.

*Cases 25-28.* Blandy also suggested that four other cases could be diagnosed in retrospect from notes in the case-books.

*Cases 29-32.* Two other suggestive cases had been seen at Napsbury and two more were seen later, all women, between the ages of thirty and seventy years.

*Case 33.* In the same year (1913), Cole (12) published a case from Bethnall House Asylum—a twenty-five year old woman with katatonic stupor who had diarrhoea and the erythema.

*Cases 34-36.* Johnstone (13) published the details of a case at Holloway Sanatorium, Virginia Water, with a note that two similar cases were seen in 1912.

*Case 37.* Rainsford (14) a case with the typical erythema on the hands, wrists, and face in a confused and delusional dement woman inmate of the Stewart Institution, Dublin.

*Case 38.* Spurgin (15) a case in which the diagnosis of acute pellagra was suggested, though there can be little doubt it was one of dermatitis exfoliativa.

The notes of the case, a Newcastle lad of twenty-one, are given in the Guy's Hospital Reports. They are here quoted, as it is amusing to read that 'Dr. Slade took specimens of pus and faeces to examine for bacteria and bacilli or evidence of simuliidae or culicoides, and of the stools for *Bilharzia R.*' (!)

Another statement made is to the effect that 'Sambon concludes that maize has nothing to do with pellagra but that it is due to the Similmur fly' (!)

*Case 39.* Lempriere (16) a case of interest in that recovery took place from a serious condition, but the subsequent history is of course not known.

A woman aged thirty-two, of Llandiloos, Glamorganshire, gave a history that four years before, in the summer, she had been taken rather suddenly ill with diarrhoea and vomiting, followed by the appearance of an erythematous rash and a little later a stuporose condition which lasted six months. The rash, which affected the face, neck, hands, and wrists and was called 'a heat rash', had recurred each summer. In 1913, when she came under observation, the erythema appeared in July, followed two weeks later by the onset of vomiting and diarrhoea with progressive weakness and emaciation, a raw condition of the tongue, and marked hyperaesthesia of the abdomen. The gait was jerky, the knee-jerks much increased, there was dorsi-flexion on plantar stimulation, but no rigidity or actual paralysis.

She was put on a diet of buttermilk and in three weeks was well on the way to recovery. The subsequent history is unknown.

*Case 40.* The last case published in 1913 was by Reid and Caldwell (17).

A farmer aged sixty-six, of Belfast, who for four successive years had had in the summer a dermatitis involving the face, chest, and hands, with soreness at the angles of the mouth. There were no mental changes, but he complained of tingling in the feet, occasional diplopia, enfeebled gait, and the knee-jerks were slightly increased.

In 1914 several other sporadic cases were recorded.

*Case 41.* Box (18) noted another case in a child.

A girl four and a half years of age came under observation with the fourth annual recurrence of an erythema affecting the face, hands, forearms,

and exposed parts of the legs. There was a coarse tremor accompanying movements of the head and upper limbs; the gait was unsteady and Rombergism was present. The mental condition was normal. There were no fits or faints, no nystagmus, no paralysis, and no sensory changes. The case passed out of observation.

*Case 42.* Willcocks (19) had under observation a case at the Royal Waterloo Hospital.

A girl of fourteen years, who had always lived in London and been well fed. The erythema was limited to the face and hands but associated with stomatitis and diarrhoea. She was normally behaved, but had several fits each day without loss of consciousness. She was ataxic and spastic, unable to stand, and showed tremor in the upper limbs; the patellar reflexes were increased, nystagmus and double optic neuritis were noted; the cerebro-spinal fluid was normal. After the erythema had disappeared and desquamation had taken place the child was again exposed to the sun's rays—erythema again appeared and the nervous symptoms were worse. The after-history is unknown.

*Case 43.* Little (20) published two cases—one in 1914, the other in 1915.

A lad aged seventeen, who in April became deeply sunburned on the face and hands and at the same time developed signs of peripheral neuritis—wrist- and foot-drop, absent reflexes, and lateral nystagmus. The heart was dilated, there was oedema of the legs, and a *B. coli* bacilluria. The cerebro-spinal fluid was normal. The case was seen by Sandwith who pronounced the skin manifestations to be typical of pellagra, but not so the affection of the nervous system. (Cohoon and Farnell—*Boston Med. Surg. Journ.*, 1913, 168, p. 50, have recorded foot-drop in eight among twenty-seven cases of pellagra.)

*Case 44.* Little also referred to another case admitted to the Sussex County Hospital from Horsham in 1913.

*Cases 45-46.* In discussion Sequeira mentioned the case of (a) a man from Essex suffering from the disease and of (b) a female child admitted to the London Hospital, the diagnosis being confirmed by Box.

*Case 47.* Pernet had also had a case in his wards.

*Case 48.* Little's second case was a boy aged twelve from Poplar.

The symptoms consisted in headache and vomiting after each meal, loose bowels, and emaciation, associated with general skin desquamation and follicular keratosis like an abortive lichen spinulosus, but without any follicular redness. On the dorsum of the hands, the nape of the neck, lower abdomen, upper parts of the thighs, and genitals there was a walnut-coloured pigmentation of the skin.

Two cases were reported from mental hospitals in 1914-1915.

*Case 49.* Ross (21); a mill-girl from Leith, an inmate of the Royal Edinburgh Mental Hospital.

She was suffering in 1912 from confusion, depression, and delusions of persecution, associated with a fine tremor of the hands and increased tendon reflexes. She recovered and remained well till the summer of 1913 when manic-depressive symptoms appeared, associated with attacks of diarrhoea, *B. pyocyaneus* being isolated from the stools. A dry, red tongue and an

eruption on the hands and face appeared in September. Later the rash disappeared, leaving some hyperkeratosis over the knuckles and knees. Marked muscular inco-ordination developed with progressive weakness, ending in death in November.

*Case 50.* Henderson (22); a woman aged fifty, admitted to the Glasgow Royal Mental Hospital 15th July 1915.

She had lived for two years on a diet of bread, tea, and a very little meat, and during the same period suffered from headache, giddiness, vomiting, sore mouth and tongue, and, during the last three weeks, tremor of the hands and difficulty in walking. During the month she was under observation she was at first excited and then depressed. The skin of the hands, wrists, and points of the elbows was thickened and rough. She complained of pain in the abdomen, but there was no diarrhoea. There was no gross loss of muscular power, but Rombergism was present and she could not walk; the reflexes were increased.

No further cases were published during the next five years. The stimulus afforded by Box's original publication had come to an end!

*Case 51.* In 1920 Wood (23) of Carolina demonstrated a case in E. Bramwell's wards at the Royal Infirmary, Edinburgh.

A woman aged fifty-two; six or seven years before she had noticed a redness of the forearms one summer; four months before weakness of the legs appeared, and at the same time typical erythematous areas were noted on the backs of the hands, on the forearms and neck, followed by sore mouth and tongue and vaginitis, but no diarrhoea. There was general muscular weakness, even involving the palate and muscles of speech and deglutition. All the tendon reflexes were abolished. There was no sensory disturbance, but there was definite diminution of the period during which tuning-fork vibration could be felt over all bony points excluding the sacrum.

*Case 52.* Low and Yellowlees (24) the same year published the case of a woman aged forty-seven, an inmate of Craig House, Edinburgh, suffering from mental depression and delusions who, though weak, showed no other symptoms till after an exposure to the sun in June, when she developed a typical pellagrous erythema of the face, hands, and wrists which cleared up seventeen days later. There was no history of diarrhoea or gastrointestinal upset at any time. The subsequent history is not recorded.

*Case 53.* In 1921 a case was recorded by Galbraith (25) from Glasgow.

A male child aged three and three quarter years; said to have been always well fed; for some months had appeared 'nervous' and easily upset; he suffered three or four giddy turns a day, these lasted half an hour during which time he had an appearance as if 'drunk'. The child was bright but shy. Nystagmus was present, the deep reflexes were increased but no clonus elicited, the plantar reflexes were dorsal in type, there was slight Rombergism, he walked briskly but trailed the left leg. Two days after admission the child became dull and apathetic, with dilated pupils, the disks were blurred and showed tortuous dilated veins, the gait was unsteady; diarrhoea and stomatitis then supervened, and ten days after admission symmetrical dry red areas appeared on the knuckles and flexor surfaces of the wrists, the tip of the nose was red and shiny, the tongue and inner lining of the cheeks became denuded and red. The blood picture was normal; the cerebro-

spinal fluid normal; W. R. negative; urine normal, indican never present; stools normal on microscopical examination and culture. The course was rapidly downhill and the child died in convulsions. The necropsy revealed nothing of note.

*Cases 54-55.* Bigland mentions two cases, the first published in 1922 (26), and the second in 1923 (27).

(a) A woman under the best conditions had suffered each spring for three successive years with loss of appetite, gastro-intestinal derangement, and nervous symptoms. The following spring a typical pellagrous dermatitis appeared accompanying a return of the previous symptoms. The author notes that her husband was employed at an asylum nearby, where cases of pellagra had occurred.

(b) Male aged fifty-nine, a house-painter out of work, sent by Dr. Hughes, seen in Liverpool. There was a history of giddiness for three months, failure of memory, and mental confusion, followed by a typical erythema on the backs of the hands and then diarrhoea. No loss of weight, appetite good, tongue normal. Beyond an increase in the knee-jerks there were no signs referable to the nervous or other systems.

Blood sugar 0.08 per cent.; blood urea 12 mg. per 100 c.c.; the urine and faeces exhibited nothing abnormal; W. R. negative; cerebrospinal fluid gave a luetic curve 1233211000.

The history suggested an inadequate diet. On a generous mixed diet with six eggs a day rapid improvement took place, the rash disappeared, the mind cleared, and the general condition improved. The subsequent history is not recorded.

*Cases 56-57.* In 1923 two cases from the Hospital for Sick Children, Great Ormond Street, London, were published by Hutchison and Pater-son (28).

(a) Female aged six years ten months, from Walthamstow; healthy till the age of three and a half years when she had an illness lasting three months, the fever and drowsiness, suggesting 'meningitis'. During convalescence an 'eczema' was noticed on the hands, feet, face, and neck. This exanthem recurred each spring and lasted for four or five months. Ten months before admission the child complained of giddiness and began to fall about. These symptoms occurred in attacks, some three attacks in two months. Four months later she was unable to walk, tremor of the upper extremities manifested itself, eyesight began to fail, and pain in the head and neck were complained of. On admission there were patches of dermatitis on the face, neck, and hands, on the inner surfaces of the arms, knees, and on the backs of the thighs. The pupils were normal, fundi normal, deep reflexes increased; cerebrospinal fluid normal; W. R. negative; no free hydrochloric acid was found in the stomach. The child died, there was no autopsy. The child had had an excellent diet except that she was very fond of cornflour and would take nearly half a pint a day. No mention is made of diarrhoea.

(b) Female aged ten years nine months, who had always lived at Acton; admitted with progressive mental deterioration and inability to walk, associated with a rash on the hands, feet, face, and neck which appeared in the spring and disappeared in the winter, all the symptoms beginning four years before. The child was emotional, delusional, and hallucinated; speech slow, gait spastic and on a broad base, reflexes exaggerated, no paralysis or

inco-ordination; the cranial nerves unaffected, eyes normal, and no alteration in sensation. There were recurring attacks of diarrhoea with the passage of offensive stools, and loss of appetite. Blood count normal; urine normal; cerebrospinal fluid normal; W. R. negative; gastric acidity about half normal. The child left hospital and passed out of observation.

*Case 58.* In 1925 Yates (29) recorded the case of a Sheffield postman diagnosed as pellagra.

In 1915 he had had vomiting, abdominal pain, and jaundice, accompanied by weakness of the legs, then attacks of diarrhoea with sore tongue, loss of weight, and a red rash on the forehead and the backs of the hands, worse in the spring and summer. In 1920, following a recurrence of jaundice, he was operated upon for the removal of gallstones and for the time being showed improvement. Later he became weaker and was admitted to the infirmary in 1924. He was unable to walk, complained of burning pains and tingling in the legs, he was tremulous and ataxic, the knee-jerks were exaggerated, the plantar reflexes flexor and abdominal reflexes present, no nystagmus, no sensory impairment. The face, neck, hands, and the extensor surfaces of the forearms were deeply 'bronzed'; there was also some pigmentation of the chest, back, abdomen, and nipples. All the organs appeared healthy and the blood picture and urine were normal. Free hydrochloric acid was absent in the stomach. Later there appeared to be some sensory impairment to all stimuli in stocking and glove areas and Rombergism became apparent. It was noted that his diet had always contained an ample supply of proteins and vitamins.

*Case 59.* Davie (30) reports (1926) the case of a maltman who for twenty years worked with, and was in the habit of chewing, barley and maize. He disliked meat and ate no fruit, but lived on bread, eggs, soups, fish, potatoes, vegetables, and tea. He had had rheumatic pains in the legs for some fifteen years, but otherwise enjoyed good health, when suddenly he became dazed, disorientated, deluded, and restless with hallucinations of hearing and smell.

After admission to the Royal Hospital, Morningside, he was kept in bed on a verandah. At the end of the summer the face and the backs of the hands were found to be pigmented and glossy as if varnished, without there having been any preceding erythema. The pupils reacted sluggishly, the knee-jerks were increased, plantar reflexes normal; W.R., blood and cerebrospinal fluid negative; blood count—red cells 3,100,000; white cells 4,200; haemoglobin 50 per cent.; polymorphonuclear 44 per cent.; lymphocytes 48 per cent.; urine normal.

By the end of the year the pigmentation had faded and did not return the following summer, though exposed to sunshine, but attacks of diarrhoea occurred. The man then developed an epithelioma of the tongue and died of broncho-pneumonia.

*Cases 60-68.* Mention is made that four cases of pellagra were under the care of Robertson at Morningside in 1921, and four more cases in 1924.

*Cases 69-70.* In 1927 MacCarthy (31) recorded the cases of two sisters, both married women in the thirties, of Coolrain, Queen's Co.

(a) Complaint of loss of energy, muscular weakness, and mental depression, associated with a rash on the hands and the forearms; the pupils were large and the knee-jerks increased, otherwise there was little to be

elicited on examination. Two weeks later there developed vulvitis, sore mouth, salivation, and diarrhoea; the dermatitis in the third week was characteristic of pellagra. There was an intense stomatitis and the woman complained of lightning pains in the legs. She died one month after coming under observation.

Inquiry elicited the fact that she had been 'odd' for some eighteen months and had had a rash on her neck for some years.

(b) There was a history of recurring dermatitis on the hands and on the neck due to sunburn each summer, with feelings of muscular weakness and dizziness. When seen she presented no signs save increased patellar reflexes.

*Case 71.* Kimber (32) has described the case of a woman aged thirty, an inmate of Hillend Mental Hospital, St. Albans (1927).

She suffered from headache, restlessness, instability, and dementia, but the physical condition was good except for some diarrhoea. Six months after admission, in the summer, she manifested thickening and pigmentation of the skin of the backs of the hands. The following December this had disappeared, to reappear the next March and disappear again in the ensuing winter. In the third spring the rash did not develop, but it was noted on 23rd August and then only lasted till the following month. The rash reappeared in the fourth year in August, followed by soreness of the tongue and diarrhoea, signs of affection of the nervous system then became manifest including choreiform movements; later convulsions occurred and death ensued. At necropsy the only thing remarked was a small atrophic bowel without ulceration.

*Cases 72-73.* Barton White and Hadfield (33), (34) published in 1927 notes of two cases, both women, inmates of the Bristol Mental Hospital.

[It should be noted that these authors are in error when they state 'In Great Britain the disease has only been reported from Mental Hospitals'.]

(a) A twenty-eight year old woman admitted in an irritable, emotional, confused state. She was thin and pale, but without physical signs of visceral disease and without neurological symptoms save dilated pupils and a fine tremor of the hands. She was treated on a verandah and then developed acute 'sunburn' of the face, neck, and hands—a dusky erythema followed in two weeks by pigmentation and later by blistering and suppuration, although after the onset she had been kept indoors.

The tongue was red and swollen and stomatitis was present, diarrhoea developed later. The stools microscopically showed nothing abnormal. Blood—red cells 4,000,000; white cells 8,000; haemoglobin 30 per cent. In spite of careful dieting emaciation was progressive and death ensued. At necropsy what was described as a thin, atrophied bowel was found.

(b) In the second case a woman aged twenty-one years; depression with delusions and anorexia followed the birth of a child.

She was admitted in February in a state of catatonic stupor. In May sunburn affecting the face, neck, and hands manifested itself, with thickening of the skin, pigmentation and scaling over the knuckles; diarrhoea supervened and death followed. There were no physical signs before death except large pupils. At post-mortem examination the walls of the bowel generally were said to be thinned, and ulceration in the last twelve inches of the colon was discovered.

*Case 74.* McGregor (35) in 1930 recorded the case of a married woman of fifty-four seen in January 1929, who had had a sunburn eruption during the previous three years which was worse in the spring and relieved in the summer.

When seen in January the exanthem was even more aggravated and affected the face, hands, arms, and elbows, all exposed surfaces, as she kept her sleeves rolled up. Appetite had failed and little had been eaten for six months. There had been no vomiting or diarrhoea.

For two years she had been mentally depressed and lately had become quarrelsome and the memory had become bad. The buccal mucous membrane and tongue were inflamed and ulcerated. There were no signs of involvement of the nervous system or of other organs. The blood picture, stools, tests of liver, and kidney function were normal.

On a diet of minced meat, eggs, milk pudding, bread and butter, cabbage, orange, marmite, 10 minims of radiosterol and 30 minims of dilute hydrochloric acid a day she rapidly improved, and in eight weeks had gained eight pounds in weight. She got quite well and became normal mentally, and when nine months later she reported, she was still in good health.

*Cases 75-6.* Parsons (36) of Birmingham mentions 'Three cases of Pellagra in one family' (1929) in the following words:

The first case 'had a rash on her legs at sixteen months and died'.

The second 'became ill at ten months old, had diarrhoea and vomiting, spasmodic movements and spastic legs. At two years and five months she was admitted to hospital, but died twenty-four hours after. The face was expressionless, there was no rash, but there were fine tremors of the hands. The lumbar puncture was normal, and nothing was found *post mortem*.'

The third case 'came under observation at two years with a rash. Six months later she came into hospital with a rash, desquamation, and incipient convulsions and spasticity. Vitamin B. was given and she improved greatly and at present seemed a normal child.'

It is not clear whether the diagnosis of pellagra was made in each case as the child came under observation or whether in the first two cases it was made in retrospect, after the third case came into hospital. Even in the third case the details, though suggestive are so meagre that it is not possible to offer an opinion on it.

Such then is a brief summary of all the isolated and smaller sporadic groups of cases of pellagra recorded in this country.

The general interest in the disease aroused in the year 1913 led also to its recognition in much larger numbers among the inmates of our asylums.

The following information has been gleaned from the Annual Reports of the Board of Control (37).

During the period 1913-18 45 deaths (39 female, 6 male) from pellagra are noted. In 1919 there were no deaths from that cause, but there were 2 in 1920 and 1 in 1921. In 1922 there were 21 deaths (18 female, 3 male). A large proportion of these cases occurred in the Lancashire County Mental Hospital, Rainhill.

In the 1913-18 period 36 cases were there diagnosed, 1 in 1921, and 14 new cases (3 male, 11 female) in 1922.

In 1923 a total of 13 cases was notified from asylums and 8 inmates

and 1 member of the staff died of the disease. The distribution of these deaths was as follows—Wakefield 2 male and 1 male nurse; Redhill 1 male, 1 female; at Chartham, Kesteven, Norfolk, and the Isle of Wight 1 female each.

In 1924 11 cases of pellagra (1 male, 10 female) were recognized, and 4 deaths (1 male, 3 female) occurred. In 1925 2 further cases were diagnosed at Rainhill, a total for that asylum, with an average of 2,100 inmates, of 56 (15 male, 41 female) since 1913.

In 1925 there were 1 male and 8 female deaths; in 1926 4 females died of the disease; in 1927 1 male, 4 females; in 1928 1 male, 4 females. The Annual Reports for 1929 and 1930 make no reference to pellagra.

In the period 1913–28 there were 104 deaths from pellagra among asylum inmates, a figure closely approximating, it would appear, to the number of cases diagnosed.

Case reports of some of the asylum cases have been published.

Watson (38) writing upon the cases at Rainhill (1923) states that the majority of the patients were between forty and fifty years of age; in some the disease was present before admission, but the majority had been resident in the asylum for from six months to several years, and one case twenty-seven years. The mental condition was generally diagnosed as melancholic or delusional. The dermatitis was typical and symmetrical, affecting the backs of the hands, the wrists, face, neck, and the skin at points of pressure. Gastro-intestinal symptoms, stomatitis, diarrhoea, were marked except in one female who recovered from her attack though the later history is not known.

The nervous symptoms were weakness, especially of the lower limbs, often of rather sudden onset with exaggerated knee-jerk, jactitation or choreiform movements of the limbs and face, and frequently a peculiar alteration of articulation.

In the majority of cases symptoms first appeared in the months of April to August, in one case in March, in another in October. The dermatitis sometimes preceded, sometimes followed, by some weeks, the other symptoms. The course of the disease, as observed at Rainhill, was from one week to two months in the more acute cases, or a few months in the remainder of the twelve fatal cases among a total of fourteen. The two who were said to have recovered were the youngest in the series, aged twenty-eight years, and only exhibited the dermatitis. These should be regarded only as having recovered from that year's attack, the probability being that they sickened again the following year.

Referring to the diet, Dr. Watson says that, in the year 1922, when this group of fatal cases occurred, it was more generous and more varied in every way especially as regards protein than in previous years.

McCowan (39) has given the histories of four asylum patients (1924). All may be considered to have been insufficiently nourished as there was a history of refusal of food.

(a) Suicidal melancholic, typical skin eruption, affection of mouth and tongue; diarrhoea—(bowel flora normal); exaggerated knee-jerks. Necropsy revealed congestion and ulceration of the large and small bowel, all other organs normal.

(b) A delusional case with hallucinations; dermatitis of the hands, wrists, face, neck, stomatitis, and vaginitis; diarrhoea; vertigo and uncertain gait, increased patellar reflexes. At necropsy all organs normal and no intestinal lesions discovered.

(c) A 'wet', destructive, hallucinated, impulsive schizophrenic after three years residence in the asylum developed a dermatitis of the hands, wrists, face, and inner sides of thighs, stomatitis, and diarrhoea with choreiform twitchings of the arms and shoulders.

(d) A female aged thirty-two, depressed with somatopsychic delusions; four months after admission developed a typical skin eruption, stomatitis, and bloody diarrhoea with rapid emaciation and death in three months. Post-mortem examination revealed ulceration of the large bowel.

#### *Addendum*

Since this article was submitted for publication two further cases of pellagra have been recorded in England.

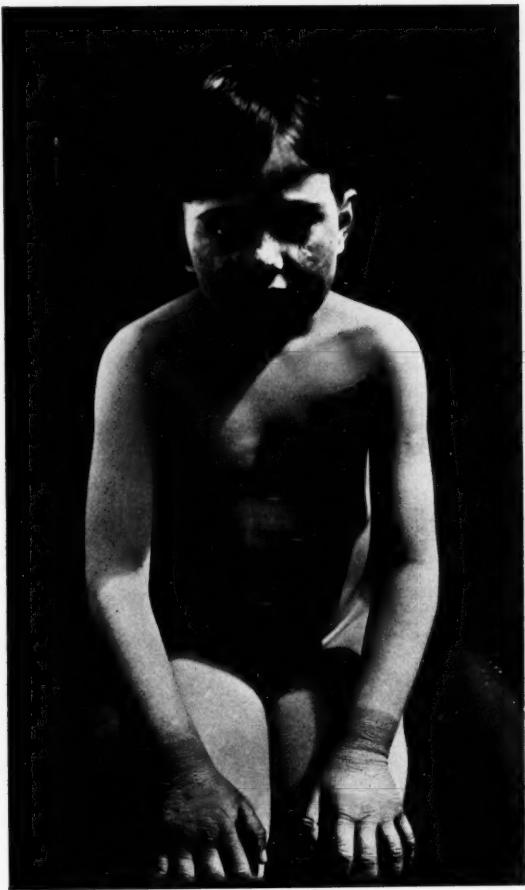
The first by Cole—*Brit. Journ. Child. Dis.*, 1933, xxx. 262—a typical case which ended fatally after leaving hospital in a female child aged eight years, the daughter of a labourer living near Cambridge whose other children aged 16, 14, 10, 6, 3, and 1 year were all healthy.

The second case by Simpson—*Proc. Roy. Soc. Med.*, 1934, xxvii. (Sect. Trop. Med. and Parasit.)—a woman aged forty-six who developed mild skin manifestations of pellagra and anaemia three years after a partial gastrectomy for duodenal ulcer when two-thirds of the stomach were removed.

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OBSERVATIONS ON THE SPEED OF THE CIRCULATION<sup>1</sup>

By C. W. CURTIS BAIN

ALTHOUGH Harvey (6) wrote of the variations in the speed in the circulating blood, and the physiologists in the nineteenth century established the fact that in animals each species has a constant circulatory rate, it was not until 1922 that Koch (7) devised a means of estimating the speed of the circulation that could be applied to man. His method was cumbersome, and the result was apt to be spoilt through the clotting of the blood. Accurate knowledge on the subject dates from 1926, when Blumgart and Weiss (1, 2) introduced their radium method. They injected a radioactive solution into the vein at one elbow and placed a detector on the other elbow, in which the particles of radium could be seen as soon as they reached the artery at that point. The time that elapsed between the injection and the appearance of the radium particles in the detector was taken with a stop-watch, and recorded in seconds. They thus obtained the time taken by the blood-stream to travel from the veins at one elbow, through the pulmonary circulation, and down the arteries to the other elbow. They called this the 'arm-to-arm' time. By placing another detector over the position of the right auricle they were able also to obtain the time spent in the veins between the elbow and the heart, which they called the 'arm-to-heart' time.

In normal subjects the average arm-to-arm time was 18 seconds. Moderate increases in the ventricular rate caused only a slight increase in the velocity. It was not diminished when the ventricular rate was slow. The rate was somewhat fast in children: it did not slow in old age.

In cases of heart disease without heart failure the rate was either normal, or slow if the heart was severely damaged. In high blood-pressure it was either normal or slow: it was never rapid. In heart failure the rate was always slow. Oedema was usually present when the time spent in the veins (arm-to-heart time) was more than double the normal.

In emphysema the times were on the fast side of the normal. Some cases had cardiac failure with only a moderate amount of slowing. In profound anaemia Blumgart, Gargill, and Gilligan (3) found that the rate was always fast and might be double the normal. In hyperthyroidism, too, the times were fast, if there was no accompanying disease of the heart, and heart failure might occur with a normal time. Conversely in myxoedema the rate was slow.

<sup>1</sup> Received August 21, 1933.

*Histamine Method*

In 1928 Weiss, Blumgart, and Robb (12) noticed that when histamine phosphate was injected intravenously, a flush appeared on the face at a constant interval after the injection. They used a 1/5,000 or 1/10,000 solution in doses of 0.001 mg. per kilo of body-weight. Simultaneous observations made with the radium method showed a close correspondence between the results obtained by the two methods. The normal average arm-to-face time with histamine was 23 seconds. This was 5 seconds longer than the arm-to-arm time obtained with the radium method, but the histamine has to pass through the arterioles to the capillaries and influence them before a flush can be seen, whereas the radium particles become visible in the detector as soon as they reach the brachial artery at the elbow.

The patient often also noticed a metallic taste in the tongue within a few seconds of the flush, which acted as a check upon the flush time. The cardiac rate increased at about the same time as the flush began, and returned to normal when the flush disappeared. Many patients experienced a throbbing headache a minute or so later, which lasted some minutes. In subjects with emphysema unpleasant symptoms of dyspnoea occasionally supervened. They were never serious, and could be promptly controlled by an intravenous injection of adrenalin. No other effects were noticed, and they all passed off in less than ten minutes.

In abnormal conditions the histamine method gave the same comparative results as the radium. In cardiovascular disease without circulatory failure the times were either normal or moderately increased. In the presence of cardiac failure they were slow. In hyperthyroidism the times were fast. In anaemia a flush was often difficult to see, but in a few cases in which it was observed the times were also fast. They consider the test is without danger. It is simple to perform and does not take long. The effect passes off quickly, and the test may be repeated in ten minutes.

*Method of administration.* On the basis of 0.001 mg. per kilo of body-weight 0.064 mg. is the accurate dose for a patient weighing 10 stone. Ampoules were therefore made up containing 0.128 mg. dissolved in 10 minims of saline. In these the accurate dose for a 10-stone patient is contained in 5 minims and is roughly in a 1/5,000 solution. The dose per stone of weight is half a minim. The ampoules have been found generally satisfactory, although individuals differ considerably in their reaction to histamine, and the doses for repeated injections may often be altered with advantage to meet differing susceptibilities.

The injection is made into the median basilic vein, and the stop watch is started immediately. The patient is warned about the metallic taste, and is told to put out his tongue as soon as he notices it. The time is noted, and, in my experience, has always preceded the flush. The stop of the watch is therefore pressed when the flush appears. This is seen first round

the eyes, and spreads rapidly over the face. The first appearance is taken as the circulation time. When the flush is definite, it is seldom that two observers who have a little experience will differ by more than a second or so. During the height of the flush the patient is often conscious of heat and flushing of the face, and may appreciate the fact that his heart is going faster. The flush lasts usually up to about 30 seconds, depending upon the intensity. Occasionally it will last longer, and may persist for two minutes. The mechanism of the prolonged flushes is uncertain. It is advisable for the patient to remain recumbent for a few minutes after the injection to lessen the risk of headache. No further precautions need be observed. In the following observations the patient has sometimes been in bed, but more often the test has been done with the patient lying on a couch during the routine cardiovascular examination.

### *Results*

In all some 300 observations have been made. Of the first 230 no satisfactory flush was obtained in 41. Of these 41 failures 17 occurred during the first two months, when special care was being taken to guard against the possibility of unpleasant reactions, and the doses employed were small. They may fairly be discarded. The remaining 24 failures were among the last 197 observations. Six patients were anaemic: two were jaundiced. Such cases would not be expected to flush well. Two had Graves' disease, and were so flushed before the injection that no additional histamine flush could be made out. There are left 14 cases out of 187 in whom no flush could be seen.

Although 90 per cent. of cases have flushed sufficiently for the time to be recorded, the number of those who flush vividly is much smaller. The flushes obtained were noted as good, fair, or faint. The number of 'good' flushes was 120: those marked fair numbered 33, leaving 36 whose flushes were faint. Out of the 189 whose flush time was taken, 65 per cent. showed good flushes, 17 per cent. flushed moderately, and in 18 per cent. the flush was faint.

Out of the total number of observations, including all the failures from every cause, the percentage of those who flushed well was just over fifty.

*Cardiac effect of histamine.* Histamine has a definite effect upon the heart, and it is usual for the cardiac rate to rise after the injection. The pulse has not been taken in this series since the attention of a single observer is occupied with the flush. For the most part the tachycardia disappears in a few seconds. When it has been more persistent it has been charted. On two occasions only has it risen above 120. In a man with rheumatoid arthritis the pulse accelerated from 78 to 140, and in another, in whom a vasomotor neurosis was engrafted upon a cardiac rheumatism, a pulse-rate of 132 before injection became 160 after it.

*Ill effects.* Out of the 189 observations in which a flush was obtained, headache was noted in 50. The proportion of patients who experienced a headache was about one in four. The pain was situated in the frontal area above the temples. It was thus of the type of the congestive headache, and was probably due to the sudden dilatation of the cerebral vessels. Pickering and Hess (10) suggest that it is due to the stretching of the meninges by the vascular dilatation. If so, it would appear to be unavoidable. In thirteen patients only was the headache severe. Once it lasted half an hour: in another case 15 minutes. Usually it passed away in a few minutes.

For single observation the headache does not influence the test. It becomes important if successive observations are made. A patient who has had a severe headache is apprehensive of the next injection. Apprehension seems to cause an outpouring of adrenalin in some people, and a constriction of the small vessels occurs which has to be overcome by the histamine. The histamine flush may therefore be delayed.

On six occasions the injection has been followed by dyspnoea. Three were patients who had heart failure with congestion. No. 24, three months previously, had had a flush-time of 38 seconds (Table X). Another test was performed since, in the interval, she had developed oedema. On this occasion she became dyspnoeic after 24 seconds, and no flush could subsequently be made out. No. 85 (Table IX) became dyspnoeic 30 seconds after the injection, and the flush began at 42 seconds. No. 101 (Table XXI) was already orthopnoeic, but the respiration became more frequent 30 seconds after the injection, and the flush followed at 45 seconds. The fourth patient, No. 36 (Table XV), developed a tender liver and crepitations at the sound base on the fifth day of pneumonia. The respirations quickened 14 seconds after the injection and the flush began at 24 seconds. The remaining two were cases of asthma, in whom a transient dyspnoea occurred soon after the flush.

Dyspnoea may be produced by histamine in two ways. In heart failure it may occur when there is engorgement of the venous system and congestion in the lungs. This type of dyspnoea always precedes the flush, and arises about the time at which the histamine might be expected to reach the lungs. It is probably due to the sudden dilatation of the already congested pulmonary vessels with a consequent diminution in the vital capacity of the lungs. In asthma the dyspnoea is probably reflex in origin, since it does not occur till after the flush has started. Both types of dyspnoea subside naturally in a few seconds.

*Severe reactions* occurred in three cases, one of whom died. A boy of three with a congenital heart and considerable cyanosis complained of headache after the injection and then he vomited. He recovered in 15 minutes without treatment. In the case of No. 85 another attempt to measure the circulatory speed was made after the heart failure had gone. She had now only a foetal rhythm. After the injection she felt ill: her pulse-rate rose

to 116 for some minutes, and it became alternating. Both the tachycardia and the alternation subsided naturally in about ten minutes.

The fatal case was a woman of 45 with advanced heart failure. She had a large heart, anasarca, a large liver and spleen. Her blood-pressure was 170-100. It was thought that she was a case of hyperpiesia in whom the pressure had fallen with the onset of heart failure. At the time the supply of histamine ampoules had become exhausted, but an old one was found, and was injected. It was without effect: there was no flush: the patient complained of nothing. During the next few days the signs of failure receded. The oedema appeared to lessen, the liver shrank. The blood-pressure fell to normal (140-90), so that the original diagnosis was doubted. On the third evening she vomited three times. The next morning a fresh supply of histamine arrived, and she was given another injection. No satisfactory flush was seen, but immediately after the injection she vomited, and seemed in considerable distress. Weiss, Blumgart, and Robb (12) found that adrenalin was an effective antidote to histamine, and a solution of adrenalin had always been kept ready in case of emergency, but it had never been necessary to use it. On this occasion two minims of adrenalin were injected intravenously. A minute later the pulse rose to 120 or more, and soon after it stopped, nor did it start again in spite of further injections of adrenalin into the heart. At autopsy great hypertrophy of the left ventricle was found. The coronary arteries were normal. There was generalized anasarca, all the subcutaneous tissues being oedematous. It seemed that the improvement in her condition was illusory. She was a pure example of hyperpiesia, and the falling blood-pressure and the vomiting both heralded an increasing failure of the heart. The immediate cause of her death was probably ventricular fibrillation following the intravenous injection of adrenalin.

Histamine injections were consequently suspended until all previous reactions had been examined. As a result no more tests were made on patients who had advanced heart failure with much oedema, although it would probably be safe except where the failure is secondary to hyperpiesia, as in this case and in No. 85. The effect of histamine on the heart is to cause a tachycardia, and a tachycardia is not well borne by a heart failing under the load of hyperpiesia. No. 85 may also have been apprehensive of the second injection since the first caused her to have dyspnoea. The combined effect of the apprehension and the histamine tachycardia may have induced the alternation. In the fatal case the heart was failing rapidly, and it was undoubtedly unwise to administer a drug which would tend in any way to increase the load. Adrenalin should not be used as an antidote to histamine in heart failure, though it may be effective in the asthmatic reaction if the dyspnoea should last long enough for it to be needed.

*Flush Times*

Although the time of the metallic taste has always been taken, it has not proved of much value. It is entirely subjective, and patients have frequently thought they noticed something before they actually did. Only the flush times have therefore been recorded.

The cases have been numbered according to the date on which the test was done. In the tables in the appendix the sex, age, weight of the patient are given with the clinical histories.

*The normal flush time.* Since diseases of the lungs, blood and disorders of the thyroid exert an influence upon the speed of the circulation, it is necessary to exclude them from consideration when ascertaining the limits of the normal. Frank cases of the effort syndrome have also been set apart. Thirty-one cases have been examined in whom the heart, blood, and thyroid were normal clinically (Table I).

With five exceptions to be described, all these patients had flush times between 19 and 25 seconds. This, therefore, appears to be the normal range. The normal point in the series is thus 22 seconds, which is 1 second faster than the average normal obtained by Blumgart. Those with pulse-rates over 100 had flush times on the fast side of the normal point. Two subjects who were over seventy years of age had flush times on the slow side. Otherwise neither age nor weight nor variation in the pulse-rate from 48 to 120 a minute had any influence upon the speed of the circulation.

Serial observations were made upon case No. 42. She was undergoing medical treatment for a gastric ulcer, and was confined to bed. The observations were made at approximately the same time each day. The patient was anxious to co-operate, but she became decidedly apprehensive of the latter injections, which always gave her a headache.

27.4.31	Pulse 84	Flush time 20 seconds
28.4.31	„ 86	„ „ 30 „
29.4.31	„ 84	„ „ 30 „
30.4.31	„ 92	„ „ 25 „
1.5.31	„ 76	„ „ 23 „
2.5.31	„ 90	„ „ 25-52 seconds

On the occasion of the last injection, which she was obviously fearing, the flush could just be seen at 25 seconds, but it did not become distinct until 52 seconds had elapsed. To the observers it seemed as if some constriction was being overcome by the dilating action of the histamine. Lewis (8) has shown that the constriction caused by adrenalin is overcome by histamine if they are both pricked through the skin. In an apprehensive patient there may be an outpouring of adrenalin with a consequent vasoconstriction. The histamine flush will then only appear when this is overcome, and the time obtained will not be an indication of the circulation speed at all.

If this reaction were common it would render the test useless. Fortun-

ately it is not, and only two cases (Nos. 70 and 95) have had flush times on the first examination which have been much slower than the clinical condition warranted.

Of the five cases with circulation speeds outside the normal range, two had flush times of 17 seconds, or 2 seconds faster than the normal limit. No. 29 complained of tachycardia after the injection, being the only case in the series to do so. His pulse was then found to be 140. He had, therefore, a degree of vasomotor instability. No. 51 is a simple case of obesity, and no reason can be given why her circulatory speed should be fast.

Of the three cases with the slow flush times, No. 16 was admitted to hospital with great intestinal distension. The blood urea was 100 mg., but he had been vomiting. He recovered completely. Unfortunately the flush time was not again estimated, as it was not appreciated at that time how close would be the normal range. No. 64 was so pigmented that a diagnosis of Addison's disease was discussed. It is probable that the flush was not seen in the pigmented skin until some seconds later than usual, and that this accounts for the apparently slow time. The test was repeated after she had rested in bed a month. It was then 26 seconds. No. 70 has been the subject of many diagnoses. She is quite incapacitated, but has no physical signs. The test was repeated after she had been in hospital a fortnight, and again a fortnight later. On the first occasion the flush time was 30 seconds; on the last it was 34 seconds. She is almost certainly an example of the adrenalin effect in a highly nervous subject.

*Effort syndrome.* Four cases have been examined. In each the times were fast (Table II).

No. 71 gave a history of increasing incapacity for some years. Recently she had been unable to walk more than a few yards. Her basal metabolic rate was normal. The heart was normal. 13.6.31. Flush time 14 seconds. Pulse 140. Three months later she returned for treatment, and was confined to bed. The following day her circulation-rate was again estimated. 29.9.31. Flush time 18 seconds. Pulse 116. After a week of massage she was allowed to get up gradually. 12.10.31. Flush time 19 seconds. Pulse 110. Exercise was increased until she could walk to do her shopping. 5.12.31. Flush time 23 seconds. Pulse 80. As she improved the circulation speed returned to normal with the pulse-rate.

*Disorders of the thyroid.* The test is unsatisfactory in hyperthyroidism as the normal flushed condition of the skin obscures that produced by histamine. In one case with a basal metabolism of +60 per cent. the flush time was 14 seconds: in three more it varied from 21 to 25 seconds (Table III). Hypothyroidism was proved by measuring the basal metabolism in one case only, but two more improved on thyroid extract. The flush times ranged from 28 to 30 seconds (Table IV).

*Anaemia.* Patients with advanced anaemia also do not flush well. Two cases of pernicious anaemia and two of a slight secondary anaemia are included. In one who had 1.8 million red cells and 42 per cent. haemoglobin

the flush time was 15 seconds: the others ranged from 19 to 22 seconds (Table V).

*Pulmonary insufficiency.* Seven cases have been examined in whom for various reasons the ventilating efficiency of the lungs has been impaired (Table VI).

Five of these had no dyspnoea on exertion. Their flush times varied from 15 to 20 seconds. Of the remaining two, No. 166, whose flush time was 25 seconds, was unable to take any exercise during a prolonged attack of asthma on account of dyspnoea. No. 53, whose time was 29 seconds, could not walk because of an arthritis of the hip. He had moisture at the lung bases.

In No. 52 (Landry's Palsy) during the course of a week the legs, arms, and trunk muscles were successively paralysed. At the time of the first test he could not turn over in bed. The intercostal muscles were acting feebly, and he had been short of breath in bed the previous day. 11.5.31. Flush time 15 seconds. Pulse 84. He recovered slowly, and in a month he could just walk without assistance. 11.6.31. Flush time 16 seconds. Pulse 94. Recovery became complete, and he returned to work. 29.1.32. Flush time 20 seconds. This case illustrates the effect of pulmonary embarrassment upon the circulation when the heart is normal. The circulatory speed is increased to compensate for the inefficient ventilation.

*Diseases of the heart.* The cases of heart disease have been grouped first according to the nature of the lesion. When there is additional disease of the lungs, blood, or thyroid it has been stated in the charts.

Ten cases have been examined in whom the cardiac lesion was slight and of doubtful pathological significance. The flush time has been normal in all (Table VII).

*Paroxysmal tachycardia.* Nine patients have either been found to have paroxysms of tachycardia, or else have given a sufficiently satisfactory history of them. In all the attacks that have been witnessed the paroxysm has been due to auricular fibrillation (Table VIII).

In two cases where the paroxysms were associated with a degree of hyperthyroidism, the flush times were 18 and 20 seconds. In the remainder they varied from 21 to 30 seconds. No patient in this group had any symptoms of heart failure.

*Hyperpiesia.* Twenty-nine cases of high blood-pressure have been examined (Table IX). In two cases only were the flush times normal. Of these No. 164 was receiving treatment for advanced arthritis of both hips. His blood-pressure had previously been taken elsewhere and had been found raised. It was thought, however, to be due to neurosis. His heart is quite normal and there is no other evidence of established hyperpiesia. No. 138 had a high pressure on the first examination, but within a fortnight it had fallen to 160-100. A year later it was 150-84.

Blumgart and Weiss (2) found that the speed of the circulation might either be normal or slow in cases of high blood-pressure. In this series a normal circulation speed has not been present in patients with established

hyperpiesia, and the test appears to have value in differentiating such cases from those in whom the raised blood-pressure is functional in origin.

Ten cases had flush times from 27 to 29 seconds. All had an established hyperpiesia with retinal changes or cardiac enlargement and mitral regurgitation. Eight were free from cardiac symptoms. Seven of these had the same flush time of 29 seconds: the eighth, whose time was 27 seconds, is the only member of the group to have a diastolic pressure of less than 100. The remaining two, with flush times of 27 seconds, had pulmonary complications, and both had symptoms and signs of cardiac failure. One, a severe case of asthma, was dyspnoeic, and had previously had oedema. The other with bronchitis had congestion of the veins in the neck and a large tender liver.

Four cases had flush times of 31 seconds. They all suffered from angina or dyspnoea on exertion. Otherwise they were similar to the preceding group.

Ten cases had flush times from 33 to 37 seconds. Four had enlargement of the liver. Two had oedema of the legs, but in one case this was due partly to the pressure of an eight months' foetus, and the other was found subsequently to have a basal metabolism of +35 per cent. Two with times of 33 seconds had no symptoms. One of these had signs of renal congestion, since he had a considerable albuminuria. The other was being kept in bed for a femoral thrombosis when the hyperpiesia was discovered during a routine examination. It is possible that she had a measure of hypothyroidism, but unfortunately the basal metabolism was not estimated, since it was not appreciated at the time how closely the results would tally. Two more had no signs or symptoms of heart failure, but they were both prevented from taking exercise by reason of a hemiplegia or an arthritis of the hip. The last three cases, with flush times of 42 seconds or over, had oedema in addition to other signs of cardiac failure.

Hyperpiesia offers a good opportunity for studying the onset of cardiac failure. There is no infection of the heart: toxæmia is absent. The findings may be summarized as follows. The speed of the circulation is slowed in established hyperpiesia, and those without cardiac symptoms have flush times of about 29 seconds. When the patient complains of dyspnoea or angina on effort, the flush times have slowed to 31 seconds. When oedema is present the flush time is over 42 seconds. Pulmonary complications or hyperthyroidism will cause the flush times to be faster than would otherwise correspond to the grade of heart failure present.

*Chronic valvular disease.* Thirty-two cases have been examined (Table X). In two the flush time was rapid. No. 83 had recently been confined to bed on account of cardiac rheumatism. His pulse had become normal before he was allowed to get up. Subsequently he developed palpitation, especially on excitement. He had no sign of heart failure, and no abnormality in rhythm. A radiogram showed that the heart was normal in size. The pulse-rate immediately after the injection rose to 160. Clinically, therefore,

he was a case of the effort syndrome superimposed upon a cardiac lesion. The flush time accords with this diagnosis. No. 117 had a secondary anaemia in addition to her mitral lesion.

Of the five patients who had normal flush times, four had no cardiac symptoms. The fifth (No. 43) has a high grade of emphysema and bronchitis. Her respiratory rate in bed was thirty. The state of her lungs makes a speed of 24 seconds totally inadequate for her, and had her heart been normal she would doubtless have had a fast time. No. 41 had recovered from an attack of rheumatic fever. He was afebrile at the time of the test. There was a systolic murmur at the apex, but the heart was not enlarged. Serial observations were made upon him at the same time and with the same precautions as in Case No. 42.

27.4.31.	Flush time	24 seconds.	Pulse	92
1.5.31.	„	25	„	100
2.5.31.	„	22	„	110
2.5.31.	„	25	„	96

This man did not get a headache from the injections, and was not apprehensive of them. There was no significant variation in the results.

Eight cases had flush times from 26 to 30 seconds. Of these, three had aortic disease, and three had mitral stenosis with auricular fibrillation or an adherent pericardium. None of them had any symptom or sign of heart failure at the time of examination. Of the remaining two, No. 82, who had a mitral regurgitation with bronchitis, complained of dyspnoea when her flush time was 29 seconds. After rest in bed her bronchitis and dyspnoea disappeared, and her flush time was 20 seconds. No. 129 had mitral disease complicated by a severe achlorhydric anaemia. On admission she had oedema and enlargement of the liver. Two days later, when the flush time was found to be 27 seconds, the liver was still palpable.

Seventeen cases had flush times from 31 to 40 seconds. Dyspnoea was complained of by all but four, and two of these (Nos. 11 and 17) were examined in bed and were not questioned about it. No. 11 had previously had oedema. No. 146, whose time was 31 seconds, complained of exhaustion. Under treatment he improved and his flush time three weeks later was 26 seconds. No. 95, whose time was 40 seconds, is the only case with a cardiac lesion in whom the test was thought to be unreliable. She is a highly nervous woman. However, she improved considerably in 1931, and in 1932 there was no gallop rhythm and the flush time was 29 seconds. Of the thirteen who had dyspnoea five in addition had signs of venous congestion. Five members of this group were seen later when they had developed oedema. Their original flush times all ranged from 36 to 38 seconds. No. 3, six months later had oedema and a flush time of 50 seconds. No. 46, a year later had oedema and a time of 45 seconds. Nos. 24, 80, and 131 also developed oedema within a year, but for different reasons their flush times were not obtained.

As in hyperpiesia dyspnoea on exertion has usually been present in those whose flush times have slowed to 31 seconds, but oedema has not developed until the flush times have slowed to more than 42 seconds.

*Myocardial disease.* Twenty-one patients have been examined in whom the lesion was predominantly myocardial (Table XI). In three of these, who all had auricular fibrillation, the flush times were normal. No. 25 was seen first in 1927 and advised to have a course of quinidine treatment. He refused on the ground that he could do heavy outdoor work without difficulty. In 1931, at the time of the test, his attitude was the same. Nos. 154 and 155 suffered from old-standing Graves' disease, and the basal metabolism of each was over +60 per cent. Both had urgent dyspnoea and No. 155 had oedema at the time of examination, and No. 154 developed it subsequently.

Of the four patients with flush times from 27 to 30 seconds three had no symptoms. The fourth (No. 111), whose time was 30 seconds, suffered from increasing dyspnoea with nocturnal attacks which eventually made her go to bed. After a few days' rest she regained her sleep, and then she would get up for a further spell. The test was done at the end of a period in bed.

All the ten cases with flush times from 32 to 40 seconds had symptoms or signs of heart failure. One had dyspnoea: four had angina. Four had enlargement of the liver, two of whom in addition gave a history of oedema. One had oedema at the time of examination, but her veins were varicose.

Four cases had flush times of 42 seconds or over. Three of these had oedema of the feet and ankles. The fourth had a flush time of 49 seconds. He is the only case to have a flush time over 42 seconds without oedema. He was, however, deeply pigmented, and it is probable that the flush did not become visible in the pigmented skin for some seconds later than it would had the skin coloration been normal.

*Coronary thrombosis.* In nine cases there has been clinical or pathological evidence of coronary thrombosis. This includes one case who also had hyperpiesia (Table XII).

In order to appreciate the changes in the circulatory rate following coronary thrombosis, it is necessary to make allowance for the variations in the underlying pathological processes. The coronary thrombosis may have been an isolated incident, and the patient may make an apparently complete recovery. Three such cases (Nos. 21, 77, 81) are included. Again, the thrombosis may occur in a heart whose coronary arteries are already the seat of widespread disease. The heart-muscle may not recover from the blow, and a progressive heart failure may ensue, leading to death in a few months. No case of this kind has been examined, but No. 101, who did not rest, developed heart failure. Yet again the coronary atheroma which caused the thrombosis may progress in course of time and lead to a return of the anginal pain or to another thrombosis. Two of the cases were of this type (Nos. 68 and 128). Lastly, the coronary thrombosis may be only a complication of some other process, such as hyperpiesia (No. 168).

No. 65 is the only case in which the patient was examined during the painful phase of a coronary thrombosis. In this case the severe pain was over, though pain was still felt down to both wrists. The flush time was 17 seconds, which is faster than the limits of the normal and 16 seconds faster than the flush times given by the same patient on two subsequent occasions after the pain had ceased. The blood-pressure at this time was a little higher than it was when the pain was over. The pulse-rate was hardly increased at all. This result suggests that, in some cases at least of coronary thrombosis, the painful phase is associated with a striking increase in the speed of the circulation. The beneficial effect of morphia is thus easily explained. In addition to controlling the pain it will tend to diminish this overaction of the heart-muscle. Its action here is specific as in acute pulmonary oedema.

No. 21 was examined two months after his attack, for which he was kept in bed three weeks. He was then complaining only of dyspnoea on exertion.

27.2.31.	Flush time	35 seconds.	Pulse	76
27.3.31.	"	33	"	72
29.5.31.	"	30	"	72

The flush times show a gradual return towards the normal, and the patient is now leading a normal life.

Nos. 81 and 77 were examined three and five years after the thrombosis. No. 81, whose flush time was 25 seconds, has no pain if he takes care. No. 77 whose time was 23 seconds has had no pain since his attack.

No. 101 had had an attack of coronary thrombosis with pain one month previously for which he had not rested in bed. Subsequently he had dyspnoea. When examined he had signs of commencing venous congestion and his lungs were emphysematous. The flush time was 29 seconds. His further course was complicated, and his later flush times will be described during the discussion on the course of heart failure.

Of those with a progressive coronary atheroma, No. 128 had an attack of thrombosis four years before. He kept free from pain until a month before examination, when it returned on any small stimulus. He was anxious about himself and had an attack while recounting his symptoms. While the pain was still present, the flush time was taken. It was 27 seconds. Fifteen minutes after the pain had ceased, the flush time was taken again. It was then 31 seconds.

No. 68 began abruptly to have anginal pain in 1924, without, however, any initial prolonged attack. He improved progressively, so that it appears likely that the cause of his pain was a thrombosis. In 1931 he was free from it, and his flush time was 22 seconds. By the spring of 1932 the flush time was 27 seconds, though he still had no definite pain. In the autumn of 1932 he had a typical attack of thrombosis with complete alteration of the electrocardiogram.

No. 163, whose flush time was 30 seconds, has had a deficient air entry

into one lung since an attack of pneumonia which has caused him to have dyspnoea. One year ago he had a prolonged attack of anginal pain for which he was kept in bed a week. Since then the dyspnoea has been more marked. He had a widespread gallop rhythm and a tender liver.

In the case of No. 168, whose flush time was 43 seconds, the coronary thrombosis was but a complication of her hyperpiesia. She was suffering from anginal attacks at the time of examination. She had heart failure with oedema. There were no signs of venous congestion.

In a coronary thrombosis the painful phase may be associated with a striking increase in the speed of the circulation. After a coronary thrombosis the flush times are slowed, but they may return to normal if recovery takes place. If dyspnoea or angina persist or return, the flush times are over 30 seconds.

*Active infections.* Four patients have been examined while they were being kept in bed for active rheumatism, and two had syphilitic myocarditis. Three children with rheumatism had flush times faster than the normal, but children have naturally an increased circulatory speed (11). No. 12 had no cardiac lesion: in No. 63 the aortic murmur was just audible four months after the onset of chorea.

In three cases the flush times were normal. No. 19 was examined at a time when the rhythm was normal except for premature contractions arising from the auricles. He had no dyspnoea, and the heart was normal in size and without murmurs. Nos. 115 and 130 are different. No. 130 had had pericarditis four years previously. For the last four months he had not been free from rheumatic arthritis. Whenever he had tried to get up he had been forced back to bed on account of fever, tachycardia, and dyspnoea. He had mitral stenosis and incompetence, and while in hospital he developed aortic regurgitation. No. 115 had been dyspnoeic for nine months, and had nocturnal attacks of urgent dyspnoea for a month. He had an active syphilitic myocarditis, with an alternating pulse, a gallop rhythm and a large heart. Allowance must be made for excitement in both these patients. No. 130 had a pulse-rate which was consistently in the neighbourhood of 120, but immediately before the test it rose to 144. No. 115 had a high blood-pressure at the time of examination, but when it had been taken before by his own doctor it was normal, and it was normal when taken by him subsequently. His pulse-rate before the test was 120, but the cardiac rate was recorded by polygram and electrocardiogram and it never fell below 105. Weiss and Ellis (13) have found that in active rheumatic infections the circulation times are normal, although the patients are dyspnoeic on any exertion. Blumgart and Weiss (2), too, noted that in some cases of syphilitic myocarditis the circulation rate was nearly normal, although the patient had urgent symptoms. Eppinger, Kisch, and Schwartz (5), finding that the cardiac output was increased in early cardiac failure, suggested that the symptoms were metabolic in origin and due to a disturbance in the acid-base balance. No. 130 had a respiratory rate in

bed of 26; yet he could lie comfortably with one pillow, a position very different to that assumed by ordinary cases of heart failure with increased respiratory rates in bed.

There is thus some reason for supposing that in active infections of the heart the speed of the circulation is faster than the clinical condition would seem to warrant, and that in these cases dyspnoea is not caused by a slowing of the circulation.

*Congenital lesions.* Of three cases with congenital cardiac lesions (Table XIV) none had any cardiac symptoms. In two the times were 23 seconds; the third was examined during an attack of asthma and the flush time was 17 seconds.

*Miscellaneous cases.* The last eight cases are difficult to fit in to any of the preceding groups (Table XV).

Three complained of substernal pain on exertion. No. 151 (flush time 22 seconds) had a normal heart, but his lungs were full of râles. The flush time suggests that the pulmonary factor was important in causing his pain, and this was borne out by his subsequent course. No. 141 (25 seconds) had pernicious anaemia, and his symptoms disappeared on treatment with liver. No. 18 (28 seconds) was emphysematous. He was rested, and three months later reported himself free from pain, and his flush time was then 23 seconds.

No. 69 (30 seconds) suffers from the pain of intermittent claudication on exertion.

No. 36 developed signs suggesting cardiac failure during the course of a pneumonia, and her flush time was found to be 27 seconds. Two days later the dyspnoea had moderated and the liver was no longer tender. The flush time was then 24 seconds. A radiogram, however, disclosed the presence of an interlobar empyema. The formation of the empyema may have been attended by some cardiac embarrassment.

No. 133 (31 seconds) gave a history of dyspnoea on exertion. The heart was normal beyond an apical systolic murmur. Rest was advised and six weeks later the flush time was 21 seconds, the pulse being 80, and the patient free from symptoms.

No. 45 will be described later, and details of the unusual case of No. 132 will be found in the appendix.

*The onset of heart failure.* In order to study the relation of the speed of the circulation to the onset of heart failure tables have been constructed with the patients grouped according as to whether they had symptoms or signs of failure. Since diseases of the lungs, blood, and thyroid themselves affect the circulation speed all cases with these complications have been excluded.

Twenty-two cases have had flush times from 25 to 30 seconds on one occasion at least during the time that they were under observation. In some this speed was found on the first examination: in others it was the best time reached as the result of treatment. None of these patients, with

one unimportant exception to be described, complained of dyspnoea or angina at the time of examination.

Serial observations were made upon three patients who had flush times of this nature.

*No. 76.* Mitral stenosis and incompetence. Adherent pericardium. 3.1.21. Flush time 26 seconds. Pulse. 70. Nine months later she returned because she was not feeling so well. 9.10.31. Flush time 30 seconds. Pulse 104. She was rested in bed for three weeks. 29.10.31. Flush time 21 seconds. Five months later she returned again because she had lately noticed dyspnoea. 17.3.32. Flush time 31 seconds. It will be noted that, when complaint is first made of dyspnoea, the flush time is 31 seconds.

*No. 105.* Mitral regurgitation. Incomplete (2-1), heart-block. 16.10.31. Flush time 27 seconds. Pulse 52. She was rested in bed for some weeks, and attempts were made to relieve the heart-block. Atropine, adrenalin, and ephedrine were all unsuccessful, although normal rhythm returned spontaneously for a short time on several occasions. 29.10.31. Flush time 27 seconds. Pulse 46. 2.11.31. Flush time 29 seconds. Pulse 45. 12.11.31. Flush time 27 seconds. Pulse 44. Eventually she was sent home, taking Lacarnol daily. She was seen again a month later. Normal rhythm had returned and an electrocardiogram showed there was no prolongation of the *P-R* interval. The mitral murmur was just audible. 8.1.32. Flush time 24 seconds. Pulse 76. With the resumption of normal rhythm the flush time becomes normal.

*No. 45.* A hunchback who would seem to fall into the class of case described by Coombs (4) in whom heart failure is caused by a nipping of the aorta by dorsal kyphosis. Dyspnoea and cyanosis. 1.5.31. Flush time 29 seconds. Rest was advised, and three weeks later she reported herself much better. 22.5.31. Flush time 25 seconds. A month later she still said she felt better, but she had not been resting. 16.9.31. Flush time 31 seconds. Pulse 80. She was admitted to hospital, and after three days in bed the test was repeated. 25.6.31. Flush time 17 seconds. Pulse 100. She was then fitted with a spinal support which, after some trouble, was made satisfactory. 16.10.31. Flush time 25 seconds. Pulse 80.

This patient is an excitable little woman. This probably accounts for the fact that she is the only case to complain of dyspnoea when her flush time on examination is less than 30 seconds. When in the ward she was upset over something and the pulse-rate was raised and the flush time was actually faster than the normal.

These cases show the variation in the speed of the circulation that may take place even though the patient complains of no symptoms. In Nos. 76 and 45 the flush time returns to normal when they are rested in bed. In 105 it does so after the restoration of normal rhythm.

*Dyspnoea* is a symptom as well as a sign. It will be noticed more easily by some patients than others. It may, indeed, be complained of by patients with the effort syndrome and fast flush times. Apart from them nineteen patients have complained of dyspnoea, but had no other sign of heart failure (Table XVI).

The two cases in whom the circulation times are normal have active infections of their hearts. In them the dyspnoea is not due to a slowing of the circulation, but is possibly toxic in origin. Of the remainder, two only have flush times that are less than 31 seconds. Of these, No. 45 has just been described: the other was examined after a week in bed, by which time she had no dyspnoea. Many other cases with flush times that were longer than 31 seconds were also dyspnoeic, but they had venous congestion or oedema as well.

Dyspnoea, therefore, may be expected when the flush time is prolonged beyond 30 seconds.

*Angina pectoris.* Ten patients were suffering from attacks of angina at the time of examination. This number includes two who also had oedema (Table XVII).

The number of cases is few, but none have a flush time of less than 31 seconds. Cardiac pain on exertion—effort angina—seems to be an alternative symptom of heart failure to dyspnoea. It appears at the same point. It is much less common. The number of those with dyspnoea in the series is 37. This is inclusive of those with signs of heart failure, but excludes cases of the effort syndrome, active infections, and those with anaemia or pulmonary complications. The corresponding total for angina is ten. The ratio is therefore one in four.

In No. 128 the flush time during an attack was found to be 27 seconds, 4 seconds faster than the time 15 minutes after the attack was over. There is thus a little evidence that cardiac pain on exertion is felt by these patients when the speed of the circulation is increased beyond the point which their heart-muscle can tolerate.

Seven patients have had flush times over 30 seconds who did not complain of dyspnoea or pain on exertion (Table XVIII).

Nos. 11 and 17, who both had severely damaged hearts, were examined in bed, and were not questioned regarding dyspnoea. No. 87, with an arthritis of his hip, and No. 136, with a hemiplegia, were unable to take exercise. Of the other three, No. 94 may have had a degree of hypothyroidism, and No. 79 had signs of renal congestion. Few cases, therefore, have flush times over 30 seconds in the absence of dyspnoea or pain on exertion.

*Venous engorgement* shows itself by the presence of congestion of the veins in the neck or by enlargement of the liver or by both. Dyspnoea on exertion may be assumed when the venous system is overfull. When the neck veins are congested there is usually orthopnea as well. No cases who had oedema at the time of examination are included in the following table (Table XIX).

Venous engorgement appears a little later than dyspnoea. Omitting the case of No. 122, in whom there was the complication of pregnancy, the circulation speed has slowed to 32 seconds when venous engorgement is present.

Eight patients have been examined who have had *cardiac oedema*. To these are added three more in whom the oedema was only partly due to heart failure. The number is small, but the test has not been often done in cases of advanced heart failure (Table XX).

No case with uncomplicated cardiac oedema has had a flush time of less than 42 seconds.

Two patients only have had flush times exceeding 42 seconds who did not have oedema (Table XXI). No. 101 had great distension of his veins which had come on rapidly and which required immediate venesection. Had the high venous pressure not been relieved it is probable that oedema would soon have appeared. No. 49 is pigmented and the recognition of the flush is likely to have been thereby delayed.

The total number of cases in the preceding tables who have had flush times of 32 seconds or over is forty-three. Of these sixteen have had venous engorgement, and twenty-seven have not. Six of the twenty-seven cases had neither dyspnoea nor angina and have already been examined in Table XVIII. The remaining twenty-one cases fall into three groups.

1. The anginal group of seven cases (Table XXII). No. 140 has been placed before among those with dyspnoea, which was his prominent symptom. He had never suffered from a definite attack of angina, but, if he tried to walk after a meal, he was pulled up by the tightness over his chest. No case with a recent history of anginal attacks has had venous engorgement.

2. Eight cases who from necessity or temperament have had their recent activities strictly controlled (Table XXIII).

3. A miscellaneous group of six cases (Table XXIV). The onset of venous congestion is not closely related to the speed of the circulation. It is not found until the circulation has slowed a little beyond the point at which dyspnoea appears, but many patients have slower times and yet have no venous congestion. They include all those suffering from effort angina, and those who for different reasons have not recently been attempting exertion.

*The course of heart failure.* Serial observations have been made upon several patients in different stages of heart failure. Two of these were cases of angina pectoris.

No. 91. Mitral regurgitation. Angina. 6.9.31. Flush time 35 seconds. Pulse 72. Frequent anginal attacks. 30.9.31. Flush time 31 seconds. Pulse 68. No attacks. 23.1.32. Flush time 31 seconds. Has remained free from attacks.

This patient was treated mainly by absolute rest followed by a gradual return to active life keeping within his tolerance. The flush times show that the improvement in the cardiac condition is slight, and the cessation of the attacks must be attributed to the diminution in his activities to which he has submitted.

No. 92. Had had angina for five years. Recently he had been experiencing many attacks daily. There was oedema of the ankles. 7.9.31. B.P. 190-110. Flush time 45 seconds. Pulse 88. With rest and digitalis

the oedema disappeared. The blood-pressure became normal. The number of attacks lessened, but they still occurred almost daily. 24.9.31. B.P. 148-70. Flush time 31 seconds. Pulse 96. A month later he died suddenly. This patient was difficult to control. His attacks were brought on by excitement as much as by exertion. It was impossible ever to abolish them as in No. 91.

*Venous congestion.* Three cases of rheumatic heart disease have been examined while they had signs of venous congestion and again after the signs had disappeared.

No.	Diagnosis.	Flush time before treatment.	Flush time after treatment.
119	Mitral stenosis, mitral and aortic incompetence. Auricular fibrillation.	13.1.32 33 secs.	21.1.32 23 secs.
122	Mitral stenosis and incompetence.	4.2.32 31 „	11.2.32 21 „
129	Mitral stenosis and regurgitation. Anaemia.	7.3.32 27 „	10.3.32 22 „

In rheumatic heart disease when venous congestion has gone, the speed of the circulation may return to normal.

In hyperpiesia, since the flush time is always slowed even where there are no symptoms of heart failure, it cannot be expected ever to return to the normal in those who have had heart failure.

Two cases only have had successive flush times taken. No. 121, who is asthmatic, had the same time of 27 seconds after a fortnight in bed. No. 139, whose flush time was 34 seconds when his liver was congested, had a time of 33 seconds after ten weeks' treatment, when his liver was no longer palpable but he was still dyspnoeic.

The following observations may be noted in myocardial and other lesions :

*No. 90.* Auricular flutter. Right bundle-branch block. History of shortness of breath and dizziness for eight days. He had vomited for the last three days. 28.8.31. Flush time 32 seconds. Pulse 136. Orthopnoea. Liver enlarged. He was treated with digitalis until the rate was controlled. He had then no dyspnoea nor was the liver palpable. 2.9.31. Flush time 22 seconds. Pulse 82 irregular. As normal rhythm did not return with digitalis, quinidine was administered and normal rhythm restored. 14.9.31. Flush time 21 seconds. Pulse regular 56.

In this case a bundle-branch block is present with a normal flush time. This is quite in keeping with his general condition, since he had experienced no inconvenience from his heart until the onset of the attack of auricular flutter.

*No. 110.* He complained of pain followed by dyspnoea during the preceding month. On examination he had a right bundle-branch block. His lungs were emphysematous and there was chronic bronchitis. The veins in the neck were congested. 9.10.31. Flush time 29 seconds. Pulse 124. He was recommended for immediate admission to hospital, but he deferred coming in for three days. On admission he had orthopnoea. The neck veins were distended even when he sat upright. The liver was palpable three inches below the costal margin, and it was tender. 12.10.31. Flush

time 44 seconds. Pulse 100. He was bled at once and given digitalis. Three days later the venous congestion had gone. The liver was no longer palpable, and he could lie flat without discomfort. 15.10.31. Flush time 23 seconds. 22.10.31. Flush time 23 seconds. A week later he died abruptly. At autopsy there was an old infarct at the cardiac apex, and a recent embolism of the left coronary artery.

This patient passed through several phases during the course of his illness. He commenced with a coronary thrombosis for which he did not rest. When he was seen first he had signs of commencing venous congestion. His time then was 29 seconds. This is the time that would be expected at such a stage in a patient with bronchitis. The venous congestion progressed during the following days until he had orthopnoea, a large liver and very distended neck veins. His flush time now was 44 seconds. This is above the usual point for the onset of oedema, and it is probable that oedema would soon have appeared had he not been relieved by venesection. Four days later he had no signs or symptoms and the flush time was normal.

No. 3 was observed through the course of three failures of the heart. His flush times are a good epitome of the variations in the speed of the circulation in heart failure. When seen first he gave a six months' history of dyspnoea. The auricles were fibrillating. The heart was enlarged; there was mitral regurgitation and aortic stenosis. The veins in the neck were congested, and he had orthopnoea. 10.11.30. Flush time 38 seconds. Pulse 130. The ventricular rate was controlled with digitalis, and normal rhythm was then restored with quinidine. 27.11.30. Flush time 28 seconds. Pulse 70 (regular). He was discharged and seen again in two months. He had kept well in the interval. The physical signs were unaltered. 5.2.31. Flush time 30 seconds. Pulse 84 (regular). 27.5.31. He was readmitted. The rhythm had become irregular about a month before. The auricles were again fibrillating. The apex impulse was  $6\frac{1}{2}$  in. to the left of the midline. The murmurs were unaltered. He was very cyanosed. The liver was palpable 3 in. below the costal margin. Oedema of the ankles was present. Flush time 50 seconds. Pulse 92 (irregular). Apex rate 132. Leeches were applied over the liver, and the rate again controlled with digitalis. Four days later the oedema had gone. The liver was enlarged 2 in. only. There was no cyanosis. 1.6.31. Flush time 41 seconds. His further improvement was slow, and it was three weeks before his liver had returned to normal, and he could be given quinidine. He required two courses each of 30 gr. a day for three days before normal rhythm was restored on 3.7.31. 9.7.31. Flush time 40 seconds. Pulse 70 and regular. Improvement was now more rapid, and the apex impulse came in 1 in. 20.7.31. Flush time 29 seconds. He was discharged and seen again a month later. He was keeping well. The pulse was 104. Blood-pressure 180-130. The physical signs were unaltered. The circulation speed was not estimated. 11.9.31. He came up again with a history of being short of breath after walking across four fields, while assisting at the haymaking. Pulse was 92, with extrasystoles. The apex impulse was again  $6\frac{1}{2}$  in. to the left of mid-sternum. The murmurs were unaltered. The liver was palpable 2 in. below the costal margin. Flush time 35 seconds. 30.3.32. He was readmitted. Pulse 96 (irregular). Auricles again fibrillating. Respiratory rate in bed was 34. There was considerable oedema of the legs and a lumbosacral pad. The

liver was enlarged 2 in. There was slight congestion of the neck veins. The lung bases were clear. Flush time 60 seconds. With limitation of fluids and salyrgan he improved a little, but after a fortnight there was still some oedema in the lumbar region. Flush time 55 seconds. Pulse 92. From this point he went downhill. No more tests were done as the histamine gave him a headache. He died on 17.6.32. At autopsy he had a large heart, with calcified aortic valves. There was generalized anasarca with free fluid in all the body cavities. The liver was large and passively congested.

This case passed through all the different phases of heart failure, and his flush times are characteristic of each. When he had no symptoms the figures were 28, 29, and 30 seconds. When he was in the stage of venous congestion his flush times were 35, 38, and 41 seconds, the last time being obtained immediately after the disappearance of oedema. When he had oedema the times were 50, 55, and 60 seconds.

The only flush time which needs an explanation is that of 40 seconds, when the rhythm had been made regular, and there were no signs of failure. This finding was in keeping with his own feelings. He felt no better, and it was only during the succeeding fortnight that improvement set in and the apex impulse shrank 1 in. towards the midline.

*The effect of pulmonary diseases upon the circulation.* In order to obtain a comprehensive idea of the effect of lung disease upon the circulation, all such cases have been included in one table. Obviously the extent of the pulmonary inefficiency will have an important bearing upon the effect of the circulation. This is hard to assess, and no attempt has been made to do so, but the pulmonary condition clinically is given (Table XXV).

Those who have no dyspnoea have flush times that lie between 15 and 20 seconds, bringing the normal point to 17 or 18 seconds. Pulmonary lesions therefore entail an increase in the speed of the circulation of roughly 5 seconds. This is borne out by the remaining cases, since dyspnoea has appeared at 24 or 25 seconds, and venous congestion at 27 seconds. That the precise acceleration will depend upon the state of the lung is obvious, and is shown by the comparison between No. 151 and No. 18, who both suffered from pain on exertion. No. 151, who had an acute but afebrile bronchitis, had a flush time of 22 seconds, whilst No. 18, who had emphysema only, had a time of 28 seconds.

#### *Discussion*

For a test to be regarded as suitable to form part of a clinical examination, it must be easy to perform single-handed, it must furnish an answer quickly, and it should be accurate within the limits of clinical observation. The histamine test fulfils the first two of these qualifications. It has also proved accurate on the whole. A nervous tachycardia will cause an increase in the flush time of a few seconds, just as nervousness will bring about a rise in the blood-pressure. Occasionally the test may be rendered valueless,

probably through an output of adrenalin. But this is rare and has only been noted on three occasions during the first examination. In most cases the flush times have accorded well with the clinical condition of the patient. Sometimes, indeed, in retrospect they have given a better indication of the true state of affairs.

An objection to the test is the headache it produces, which occurs in about one quarter of all cases. Sometimes the most phlegmatic individual will get a severe headache, while many nervous subjects have noticed nothing. No means have been found of obviating it. The headache may prevent the successful repetition of the test owing to apprehension on the part of the patient. It has no influence upon the first result.

The test has been found of use in many ways. A patient may be referred on account of some symptom of doubtful cardiac origin. A normal circulatory speed will strengthen the opinion that the heart is not at fault. Another may be seen after a coronary thrombosis. The flush time will be of assistance in assessing the amount of recovery that has taken place. Similarly it may be used to grade the efficiency of the heart after a heart failure has been surmounted. When the signs of failure are present it may occasionally help by pointing to an unsuspected complicating factor, such as hyperthyroidism.

Finally, it has afforded a new method of approach to the classification of cases of heart disease. This method, although it involves a departure from the views of some, seems to give a clear picture of the progress of events in cardiac failure. It will be discussed under the headings of the cardiac reserve, the advent of dyspnoea and effort angina, and, lastly, the onset of venous congestion and oedema.

*Cardiac reserve.* The histamine flush test shows that patients with cardiac lesions who have no symptoms or signs of heart failure fall into two groups. They may have normal flush times. The heart then is fulfilling its function normally, and the reserve is intact. They may have flush times which are prolonged to 30 seconds, or 5 seconds beyond the normal limit. Times of this kind are found generally in established hyperpiesia, in free aortic regurgitation, and in myocardial lesions. Such patients have a measure of cardiac insufficiency; the reserve is impaired, and they need to curtail their activities.

*Dyspnoea and effort angina.* Recent writers have divided heart failure into congestive and anginal types. Congestive failure is said to occur in those patients who start with dyspnoea and pass on to venous congestion and oedema. Those with anginal failure suffer from anginal attacks and eventually die in one. Now it is true that patients, while they are experiencing attacks of angina on effort, do not have venous congestion, but they may certainly, if they live long enough, have oedema. Patients complain of dyspnoea or pain when their flush times have slowed to the same point, namely, to 31 seconds. It is suggested that dyspnoea and effort angina should both be regarded as symptoms of cardiac failure, having the

same meaning, that the heart has failed to keep pace with the needs of the the circulation.

*Venous congestion and oedema.* The term 'congestive failure' has been used to cover both venous congestion and oedema, the assumption being that they are both due to one and the same process. This is at variance with the evidence of the histamine flush test. The solution of the long controversy between the back pressure and the 'vis a tergo' schools would seem to be that both were wrong in attempting to explain venous congestion and oedema on one basis.

Oedema is an almost constant finding when the flush times have slowed to 42 seconds, and this is in general agreement with the conclusions of Blumgart and Weiss, using the radium method. Unless there are complicating extracardiac factors, it does not occur before that point. It is directly related to the slowing of the blood-stream. As Mackenzie (9) said: 'The blood passes through the capillaries at a slow rate, impairs their nutrition, and allows transudation to take place which we call dropsy.'

It is otherwise with venous congestion. Venous congestion may come when the flush times have slowed to 32 seconds, which is 10 seconds earlier than the point of onset of oedema, and shortly after the stage at which dyspnoea appears. On the other hand, many patients have slower times and yet have no clinical evidence of venous congestion. In some, indeed, oedema of the feet is the first signs of failure to be noticed. These cases may be divided into two groups: there are those suffering from anginal attacks, and those who have had their recent activities restricted either by intercurrent disease or through the advice of their doctor, or by their own good sense.

Venous congestion seems to arise in those who suffer a sudden deterioration in the cardiac efficiency at a time when their circulation is already slowed. The most common cause is the onset of auricular fibrillation in a previously diseased heart. Other patients may disregard the warning sign of dyspnoea and persist in exertion in spite of it. In them the immediate cause of the congestion may be a dilatation of the heart. Indeed, it is so usual to observe clinically that the heart shrinks as venous congestion disappears that it is possible that a dilatation of the heart invariably accompanies the onset of congestion. Venous congestion may also be brought on by an attack of bronchitis, which has much the same effect upon the speed of the circulation as exertion. It is not found in those suffering from anginal attacks, since the pain stops the exertion at once, and the heart is thereby protected. The same principle will apply to those who are unable to take exercise by reason of a hemiplegia or arthritis.

If the blood has been travelling at a certain rate and the heart suddenly becomes less efficient, the situation is analogous to a car which is being driven at a fair speed when the foot is suddenly withdrawn from the accelerator. The momentum of the car will then for a time drive the engine. The circulating blood cannot drive the heart so it must accumulate behind

it. If the heart has sufficient reserve it will increase the force of its contractions, but if the speed of the circulation is already slow and the reserve is nearly exhausted, it may be unable to transmit the blood which is returning to it. The blood will then be dammed back in the veins. As the volume of the blood is much greater in the systemic circulation than in the pulmonary, the engorgement will affect mainly the great veins and the liver. Evidence of this distribution may be seen in any autopsy on a case of sudden death from heart failure, when the right auricle and the venae cavae will be found to be distended with blood.

It would be advantageous to revise the terms in vogue in describing heart failure. Cardiac insufficiency might be used to denote that the speed of the circulation was slowed. Congestive heart failure should be reserved for those cases showing congestion of the veins in the neck or enlargement of the liver. Pulmonary congestion would similarly denote congestion in the pulmonary circuit. Heart failure with oedema would be suitable for cases with oedema, while congestive failure with oedema would signify that venous congestion and oedema were both present.

#### *Summary*

1. The time taken by the blood to travel from the arm to the face in normal subjects, as shown by the histamine flush test, is 22 seconds. The normal range is from 19 to 25 seconds.

2. The flush times are fast in hyperthyroidism, in the effort syndrome, in advanced anaemia, and in diseases of the lung.

3. In the diseases of the heart some patients have had normal flush times: they have not been incommode by their hearts. Others, who yet had no symptoms, have had flush times from 25 to 30 seconds. They may be regarded as having a measure of cardiac insufficiency.

4. Dyspnoea and effort angina appear when the flush times have slowed to 31 seconds. It is suggested that dyspnoea and effort angina should each be regarded as alternative symptoms of cardiac failure.

5. Venous congestion is found in about half of those whose flush times are 32 seconds or more. The remainder include those suffering from anginal attacks, and those who have been prevented from over-exerting themselves.

6. Oedema is an almost constant finding in those whose flush times are 42 seconds or more.

7. The above figures only apply when the lungs, blood, and basal metabolism are normal. When heart failure is complicated by pulmonary diseases, advanced anaemia, or hyperthyroidism, the flush times are faster. Corresponding to the grade of failure, the heart will be less severely damaged than would be the case if these complications were absent, and great improvement may be expected if they can be removed.

Some of the early tests were performed at St. James's Hospital, Leeds. My thanks are due to Dr. Dick, and to Dr. Rawdon Veale and Professor Vining for granting me access to cases under their care. I am also indebted to Dr. Yeoman for a series of cases with normal hearts examined at the Royal Bath Hospital, Harrogate. It is a pleasure, also, to record my gratitude to Dr. Parkinson and to Dr. Terence East for their valuable criticisms during the course of preparation of this paper, although this does not in any way involve their agreement with all the views expressed in it.

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## APPENDIX

TABLE I

No.	Sex.	Age.	Weight.	Pulse.	Flush time.	Diagnosis.
			st.		secs.	
29	M	28	8	78	17	Rheumatoid arthritis.
51	F	46	15½	86	17	Obesity.
28	M	48	11	108	19	Fibrositis.
161	M	50	10½	88	19	Normal. History of oedema of legs. Diagnosed as malingering.
35	M	13	5	120	20	Schonlein's purpura.
42	F	37	7½	84	20	Gastric ulcer.
125	F	9	4½	96	20	Chronic tonsillitis.
147	M	65	15½	76	20	Syphiliphobia.
170	F	21	8	100	20	Goitre with dental sepsis.
26	M	65	10	96	21	Arthritis of hip.
27	M	42	9	78	21	Old rheumatoid arthritis.
31	F	37	8	90	21	Fibrositis.
62	F	31	9	104	21	Neurasthenia.
107	F	31	11	108	21	Cardiac neurosis.
162	F	41	10	88	21	Normal.
1	F	42	7½	80	21	Fibrositis.
2	F	22	8½	82	21	Neurosis.
34	F	30	10	108	22	Rheumatoid arthritis.
97	M	58	11½	80	22	Intercostal fibrositis.
109	M	36	12	64	22	Normal.
72	M	32	10	48	23	Post-pneumonic bradycardia.
6	F	25	9	82	24	Afebrile pyelitis.
54	M	71	13½	84	24	Sinovitis of knee.
99	M	42	10½	80	24	Old duodenal ulcer.
32	F	51	9	78	25	Infective arthritis.
56	M	43	14½	72	25	Neurasthenia.
58	M	42	13	92	25	Enlarged liver with cholecystitis.
75	M	75	10	56	25	Normal.
16	M	38	11	90	28	Intestinal distension. Blood urea = 100 mg.
64	F	67	8½	80	28	Previous ascites. Liver and spleen palpable. Pigmented.
70	F	56	6	116	36	Neurosis.

TABLE II

No.	Sex.	Age.	Weight.	Pulse.	Flush time.	Diagnosis.
			st.		secs.	
71	F	41	7	140	14	Exhaustion and dyspnoea on any exer- tion. Heart normal.
100	F	49	6	128	15	Dyspnoea and tachycardia on any exer- tion. Heart normal.
148	M	21	11	112	16	Dyspnoea and pain on exertion. Heart normal.
160	F	34	8	150	17	Attacks of tachycardia. Heart normal.

TABLE III

No.	Sex.	Age.	Weight.	Pulse.	Flush time. secs.	Diagnosis.
158	F	28	10 <sup>st.</sup>	108	14	Graves' B.M.R. + 60 %.
5	F	28	6 $\frac{1}{2}$	68	21	Graves' after hemithyroidectomy.
126	F	21	8	124	23	Graves'.
47	F	50	6	120	24	Graves' B.M.R. + 22 %.
47	A month later				25	Graves'.

TABLE IV

No.	Sex.	Age.	Weight.	Pulse.	Flush time. secs.	Diagnosis.
30	F	57	11 <sup>st.</sup>	90	29	Menopausal arthritis. B.M.R. - 9 %.
116	F	57	10 $\frac{1}{2}$	68	28	Slight cyanosis.
22	F	64	10	80	30	Cyanosis of extremities. Heart normal clinically.

TABLE V

No.	Sex.	Age.	Weight.	Pulse.	Flush time. secs.	Diagnosis.
38	F	57	7 $\frac{1}{2}$ <sup>st.</sup>	76	15	Subacute combined degeneration. Red cells 1.8 million. Haemoglobin 42 %.
20	F	43	8 $\frac{1}{2}$	90	20	Addison's anaemia. Red cells 2.7 million. Haemoglobin 53 %.
20	A month later				19	
74	F	35	10 $\frac{1}{2}$	76	21	Slight secondary anaemia.
39	M	38	12 $\frac{1}{2}$	—	22	Previous haematemesis. Slight secondary anaemia.

TABLE VI

No.	Sex.	Age.	Weight.	Pulse.	Flush time. secs.	Diagnosis.
52	M	31	11 <sup>st.</sup>	84	15	Landry's paralysis.
78	F	45	10	96	18	Asthma with râles present over both lungs.
104	F	30	9 $\frac{1}{2}$	100	19	Asthma. Some râles present.
145	M	49	13	90	19	Emphysema.
169	M	52	10	72	20	Bronchiectasis.
166	M	57	10 $\frac{1}{2}$	84	25	Asthma with râles present over lungs.
53	M	73	11 $\frac{1}{2}$	—	29	Dyspnoea. Emphysema. Crepitations at lung bases. Arthritis of hip.

TABLE VII

No.	Sex.	Age.	Weight.	Pulse.	Flush time. secs.	Clinical condition.
66	F	51	8 $\frac{1}{2}$ <sup>st.</sup>	110	19	Frequent multi-focal extrasystoles.
171	F	25	9	80	20	Slight mitral regurgitation.
86	M	66	13 $\frac{1}{2}$	84	23	Slight mitral regurgitation.
102	M	65	11 $\frac{1}{2}$	60	23	Auricular extrasystoles.
118	F	41	8 $\frac{1}{2}$	90	23	Slight mitral regurgitation.
123	M	31	9	60	23	Post influenzal right ventricular extrasystoles.
96	M	65	12 $\frac{1}{2}$	76	24	Slight mitral regurgitation.
134	M	57	—	76	25	Ventricular extrasystoles.

TABLE VIII

No.	Sex.	Age.	Weight.	Pulse.	Flush time.	Clinical condition.
			st.		secs.	
150	M	44	11	84	18	Examined during a paroxysm of auricular fibrillation (E.C.G.) B.M.R. taken subsequently + 14 %.
57	F	19	6	116	20	Toxic adenoma. History of paroxysms of tachycardia.
55	M	38	8½	130	21	Taken immediately after the cessation of a long paroxysm of auricular fibrillation.
142	F	50	9½	80	24	History of paroxysms of tachycardia. Heart normal.
84	M	19	10	56	25	History of paroxysms of tachycardia. Heart normal.
112	F	37	12	78	25	History of paroxysms of tachycardia. Slight mitral regurgitation.
44	M	71	14½	60	29	Paroxysm of auricular fibrillation in 1923 (E.C.G.).
157	F	55	—	88	29	History of paroxysms of tachycardia. Some mitral regurgitation.
167	M	60	17	68	30	Frequent short paroxysms of auricular fibrillation (E.C.G.). Cyanosis.

TABLE IX

No.	Sex.	Age.	Weight.	Pulse.	Flush time.	Clinical condition.
			st.		secs.	
164	M	66	12	80	20	B.P. 180-108.
138	M	66	14	100	24	B.P. 220-118. Atheroma of aorta.
120	F	66	9½	64	27	B.P. 195-95.
121	F	47	7½	88	27	B.P. 220-110. Dyspnoea. Asthma. Previous oedema.
108	M	60	11½	92	27	B.P. 190-115. Heart enlarged. Liver large and tender. Congestion of neck veins. Bronchitis.
73	F	64	—	94	29	B.P. 200-130. Retinal arterial changes. Foetal rhythm.
50	F	51	14½	90	29	B.P. 210-105. Mitral incompetence. T I and II inverted.
59	F	71	12	68	29	B.P. 210-110. Mitral regurgitation. Retinal haemorrhage.
60	F	51	—	84	29	B.P. 200-105.
127	M	60	10½	56	29	B.P. 266-140. Mitral regurgitation.
152	F	49	12	56	29	B.P. 220-110.
173	M	61	13	68	29	B.P. 190-115. Heart enlarged. Gout. Renal calculi.
89	F	58	—	92	31	B.P. 180-110. Cardiac pain and dyspnoea.
103	M	67	10	76	31	B.P. 200-96. Mitral regurgitation. Notching of R wave. Cardiac pain for one month.
110	M	72	9½	68	31	B.P. 200-120. Auricular fibrillation. Dyspnoea. Retinal haemorrhage.
113	F	65	11	72	31	B.P. 220-120. Cardiac pain.
94	F	60	11	86	33	B.P. 200-110. Femoral thrombosis.
79	M	48	13	84	33	B.P. 180-116. Albuminuria.
159	F	67	9	92	33	B.P. 230-130. Mitral regurgitation. Dyspnoea. Liver tender. Subacute combined degeneration. Red cells 2·8 million. Haemoglobin 64 %.

TABLE IX (continued)

No.	Sex.	Age.	Weight.	Pulse.	Flush time.	Clinical condition.
			st.		secs.	
40	M	55	11	88	34	B.P. 190-120. Liver large and tender.
67	M	69	8	80	34	B.P. 255-170. Large heart. Gallop rhythm. Intraventricular block. Liver large. Previous oedema.
139	M	50	11	104	34	B.P. 255-170. Large heart. Dyspnoea. Liver palpable and tender.
8	F	46	9	90	35	B.P. 215-120. Oedema of legs (eight months pregnant). Congested lung bases.
174	F	46	7	101	35	B.P. 230-125. Large heart. Gallop rhythm. Oedema of legs. B.M.R. + 35 %.
87	M	68	17	76	36	B.P. 200-100. Arthritis of hip.
136	M	57	10½	74	37	B.P. 260-170. Large heart. Chronic interstitial nephritis. (C.S.F. urea = 138 mg.) Cerebral softening with hemiplegia. Three attacks of unconsciousness during last eighteen months—unable to walk since the second.
85	F	64	10	90	42	B.P. 240-160. Foetal rhythm. Liver enlarged. Crepitations at lung bases. Oedema of ankles.
168	F	66	9	112	43	B.P. 178-124. Coronary thrombosis a year previous. Large heart. Gallop rhythm. Oedema of ankles. Return of anginal attacks 14 days previously.
98	M	45	10	96	46	B.P. 210-150. Large heart. Foetal rhythm. Cyanosis. Liver enlarged. Oedema to thighs. Lumbosacral pad.

TABLE X

No.	Sex.	Age.	Weight.	Pulse.	Flush time.	Clinical condition.
			st.		secs.	
83	M	23	9	132	16	Mitral and aortic regurgitation. Rheumatic fever three months before. Effort syndrome.
117	F	19	9	90	18	Mitral regurgitation. Anaemia. Haemoglobin 60 %.
33	F	23	8½	90	19	Mitral stenosis. Subacute rheumatism.
172	F	40	8	96	22	Mitral stenosis.
41	M	34	9½	92	24	Mitral regurgitation. Subacute rheumatism.
135	M	62	11½	68	24	Early mitral and aortic regurgitation. Extrasystoles. Motor aphasia probably due to an embolus.
43	F	74	8	106	24	Mitral regurgitation. Chronic bronchitis and emphysema. Dyspnoea.
76	F	28	8	70	26	Mitral stenosis and regurgitation. Adherent pericardium.
129	F	40	8½	100	27	Mitral stenosis and regurgitation. Dyspnoea on exertion for some years. Recent oedema. Liver palpable and tender. Achlorhydric anaemia. Red cells 3½ million. Haemoglobin 35 %.

TABLE X (continued)

No.	Sex.	Age.	Weight.	Pulse.	Flush time.	Clinical condition.
			st.		secs.	
15	M	57	—	68	27	Aortic stenosis and regurgitation. Heart enlarged. T I inverted. Interpolated extrasystoles.
48	F	16	8½	104	28	Adherent pericardium.
82	F	63	8½	108	29	Mitral regurgitation. Chronic bronchitis. Dyspnoea.
13	F	45	9½	92	29	Mitral stenosis and regurgitation. Auricular fibrillation.
14	F	59	9½	80	29	Aortic incompetence.
4	F	45	11	82	30	Aortic incompetence.
146	M	50	10½	52	31	Mitral and aortic regurgitation.
165	F	66	14½	72	31	Mitral regurgitation. Dyspnoea.
122	F	34	9½	84	31	Paroxysm of fibrillation during sixth month of pregnancy. On examination six days later: rhythm normal. Mitral stenosis and regurgitation. Crepitations at both lung bases. Liver tender.
153	M	77	12½	—	31	Mitral regurgitation. Alcoholic portal cirrhosis. Oedema of ankles.
176	M	64	17½	80	32	Aortic regurgitation. Dyspnoea with nocturnal attacks.
119	F	20	9½	80	33	Mitral stenosis and regurgitation. Aortic incompetence. Auricular fibrillation. Heart large. Liver palpable and tender.
144	M	46	—	100	34	Mitral stenosis. Auricular fibrillation. Dyspnoea. Previous jaundice.
114	F	73	7½	100	35	Mitral regurgitation. Dyspnoea. Liver palpable.
11	F	49	12	85	35	Mitral stenosis. Auricular fibrillation. History of oedema.
17	F	67	7	60	35	Mitral stenosis and regurgitation. Aortic incompetence. Auricular fibrillation. Jaundice.
80	F	19	7	100	36	Cardiac rheumatism some years before, followed by dyspnoea on exertion. Three months ago second attack of rheumatic fever. No walking since this attack. Large heart. Mitral stenosis and regurgitation.
46	M	33	10	—	37	Mitral stenosis and regurgitation. Aortic stenosis and incompetence. Dyspnoea.
137	F	76	9½	96	37	Heart enlarged. Dyspnoea. Cyanosis. Crepitations at lung bases.
3	M	54	10	130	38	Aortic stenosis. Mitral regurgitation. Auricular fibrillation. Congestion of neck veins. Orthopnoea.
131	F	68	11½	84	38	Mitral regurgitation. Osteoarthritis of knees. Dyspnoea.
24	F	49	8½	84	38	Mitral stenosis and regurgitation. Aortic stenosis and incompetence. Auricular fibrillation. Liver large, pulsatile, and tender.
95	F	64	10½	84	40	Mitral regurgitation. Gallop rhythm. Heart enlarged.

TABLE XI

No.	Sex.	Age.	Weight.	Pulse.	Flush time. secs.	Clinical condition.
154	F	52	st. 8	120	20	Old-standing Graves' disease. B.M.R. 70 %. Large heart. Auricular fibrillation. Confined to bed for six weeks.
25	M	47	12½	84	21	Auricular fibrillation.
155	F	40	7½	136	23	Old-standing Graves' disease. B.M.R. +66 %. Large heart. Auricular fibrillation. Oedema of ankles.
105	F	42	9½	52	27	Heart block (2-1). Mitral regurgitation.
7	M	74	12	84	30	Auricular fibrillation.
111	F	64	8½	84	30	Large heart (B.P. 180-90). Nocturnal dyspnoea. Splintering of T wave in Leads I and II.
143	M	61	14	80	30	Flattened T waves Leads I and II.
90	M	59	12½	136	32	Auricular flutter. Right bundle-branch block. Orthopnoea. Liver palpable and tender.
177	M	72	13	76	32	Mitral regurgitation. Intraventricular block. Angina.
88	M	50	—	104	32	Large heart. Right bundle-branch block. Auricular fibrillation. Dyspnoea.
156	M	66	10	68	33	Large heart. Right bundle-branch block. Dyspnoea. Liver palpable.
91	M	57	12½	72	35	Mitral regurgitation. Angina.
93	M	54	8	84	35	Mitral regurgitation. Angina.
175	M	68	12½	76	38	Angina.
61	F	51	16	100	39	Large heart. Auricular fibrillation. Oedema of ankles (varicose veins).
106	F	55	12½	44	39	Inversion of T I and II. Coupled rhythm due to extrasystoles. Liver palpable. History of oedema.
37	M	66	10	72	40	Inversion of T I, II, and III. Mitral regurgitation. Liver enlarged. Previous oedema with hydrothorax.
23	F	56	12½	84	42	T I and II inverted. Mitral regurgitation. Oedema of ankles.
92	M	78	12	88	45	Mitral regurgitation. Heart enlarged. T I and II inverted. Angina. Oedema of ankles.
149	M	68	—	88	48	Auricular fibrillation. Mitral regurgitation. Oedema of ankles. Dyspnoea.
140	M	71	13	88	49	Large heart. Right bundle-branch block. Auricular fibrillation. Dyspnoea and pain on exertion. Pigmented.

TABLE XII

No.	Sex.	Age.	Weight.	Pulse.	Flush time.	Clinical condition.
			st.		secs.	
65	M	66	11	80	17	Angina on effort for some years. One year previously the apex impulse was in the nipple line, and there was mitral regurgitation. T wave was inverted in Leads I and II. During a walk in the afternoon the pain came on severely and persisted for half an hour. He ate some dinner though still feeling the effects of the pain. At 2.30 a.m. he woke with severe pain radiating down both arms, which lasted two hours. An hour later he had another attack lasting until he was examined at 11.45 a.m. The pain was then no longer severe. He was sitting up in bed and was not restless. B.P. 180-90. Apex one inch outside nipple. Mitral regurgitation.
				72	33	Taken two days later. B.P. 135-72.
				72	33	Taken fourteen days later. B.P. 145-72.
68	M	65	14	68	22	Coronary thrombosis seven years ago. Heart enlarged. Atheroma of aorta.
77	M	72	10	—	23	Coronary thrombosis four years ago.
81	M	59	10	90	25	Coronary thrombosis three years ago. Heart enlarged. T wave inverted.
101	M	62	9½	124	29	Cardiac pain a month ago, followed by dyspnoea. B.P. 160-100. Right bundle-branch block. Congested neck veins. Emphysema and bronchitis. He was admitted to hospital where at first he improved, but later died suddenly. At autopsy the lungs were emphysematous. There was an old infarct at the cardiac apex with a large thrombus attached to the endocardial surface. The left coronary artery was blocked near its source by a recent embolus.
163	M	66	—	92	30	Coronary thrombosis 1½ years ago. Dyspnoea. Gallop rhythm. Liver palpable and tender. Fibrosis left lung.
128	M	53	10	84	31	Coronary thrombosis four years ago. Return of anginal attacks during last month. Apex impulse outside nipple. T wave inverted in Leads II and III.
21	M	55	12	76	35	Coronary thrombosis two months ago. Dyspnoea. Heart enlarged. Coronary T wave.

TABLE XIII

No.	Sex.	Age.	Weight.	Pulse.	Flush time.	Clinical condition.
			st.		secs.	
12	F	13	4½	—	16	Chorea.
10	F	16	8	—	18	Mitral stenosis.
63	F	13	—	92	18	Aortic incompetence. Chorea.
130	M	17	9	144	21	Mitral stenosis and regurgitation. Active endocarditis of aortic valves. Dyspnoea. Rheumatic arthritis of knees and shoulder. Fluctuating temperature up to 100° F.
19	M	67	11	76	22	Paroxysms of auricular fibrillation and flutter. W.R. positive.
115	M	42	10	120	24	Dyspnoea on exertion nine months. Nocturnal attacks for three weeks. Pulsus alternans (polygram). B.P. 184-114. Apex impulse heaving and outside nipple. First sound at apex reduplicated. W.R. strongly positive.

TABLE XIV

No.	Sex.	Age.	Weight.	Pulse.	Flush time.	Clinical condition.
			st.		secs.	
49	M	53	11	90	17	Patent septum. Asthma with râles present.
9	M	44	11	68	23	Patent septum.
124	M	55	9	84	23	Patent septum.

TABLE XV

No.	Sex.	Age.	Weight.	Pulse.	Flush time.	Clinical condition.
			st.		secs.	
151	M	49	—	80	22	Pain across the chest on exertion. Bronchitis. Heart normal.
141	M	59	—	88	25	Pain and dyspnoea on exertion. Mitral regurgitation. Pernicious anaemia. (Red cells 2·7 million; haemoglobin 57 %).
36	F	37	—	116	27	Pneumonia, suddenly developed urgent dyspnoea, tenderness over the liver, and crepitations at the base of the second lung.
18	M	63	10	64	28	Cardiac pain. Emphysema.
45	F	34	8½	—	29	Angular kyphos of upper dorsal spine.
69	M	69	11	68	30	Dyspnoea and cyanosis.
						Thrombo-angiitis obliterans. Heart slightly enlarged.
133	F	56	—	96	31	Dyspnoea on exertion. Slight mitral regurgitation.

TABLE XV (*continued*)

No.	Sex.	Age.	Weight.	Pulse.	Flush time. secs.	Clinical condition.
132	M	38	st. 13	100	39	Sudden attack of pain across chest ten days after operation for umbilical hernia. Subsequently respirations were increased to 24, and he was pale and cyanosed. Five days later he could lie comfortably with one pillow. Pulse 100, of small volume. B.P. 90-70. Apex impulse not palpable. Percussion dullness extended two inches to right of sternum. Heart sounds distant. Systolic murmur maximum just to the left of the sternum. No thrill. No signs of venous congestion. The following day he died, and at autopsy, for details of which I am indebted to Dr. C. H. Greenwood, the right auricle was much dilated. The right ventricle was dilated, and contained much grey fibrinous clot which was adherent to the ventricular wall and to the tricuspid valves. In the sub-peritoneal tissue deep to the sutured hernia was a soft breaking down area. Diagnosis: intra-cardiac thrombosis.

TABLE XVI

No.	Pulse.	Flush time. secs.	Clinical condition.
130	144	21	Active rheumatic endocarditis.
115	120	24	Active syphilitic myocarditis.
45	—	29	Kyphosis of spine.
111	84	30	Myocardial disease.
76	70	31	Mitral stenosis. Adherent pericardium.
110	68	31	Hyperpiesia. Auricular fibrillation.
133	80	31	Slight mitral regurgitation.
165	72	31	Mitral regurgitation.
176	80	32	Aortic regurgitation.
88	104	32	Right bundle-branch block. Auricular fibrillation.
144	100	34	Mitral stenosis. Auricular fibrillation.
21	76	35	Coronary thrombosis two months previously.
80	100	36	Mitral stenosis and incompetence.
46	—	37	Mitral stenosis and incompetence. Aortic stenosis and incompetence.
137	96	37	Mitral regurgitation.
131	84	38	Mitral regurgitation.
132	100	39	Intracardiac thrombosis.
95	84	40	Mitral regurgitation. Gallop rhythm.
140	88	49	Right bundle-branch block. Auricular fibrillation. Pigmented.

TABLE XVII

No.	Pulse.	Flush time.	Clinical condition.
		secs.	
89	92	31	Hyperpiesia.
103	76	31	Hyperpiesia.
115	72	31	Hyperpiesia.
128	84	31	Old coronary thrombosis. Recurrence of angina.
177	76	32	Mitral regurgitation. Intraventricular block.
91	72	35	Mitral regurgitation.
93	84	35	Mitral regurgitation.
175	76	38	—
168	112	43	Hyperpiesia. Old coronary thrombosis. Recent recurrence of angina. Oedema of ankles.
92	88	45	Mitral regurgitation. Oedema of ankles.

TABLE XVIII

No.	Pulse.	Flush time.	Clinical condition.
		secs.	
146	52	31	Mitral incompetence. Early aortic incompetence.
79	84	33	Hyperpiesia. Albuminuria.
94	—	33	Hyperpiesia. Femoral thrombosis.
11	85	35	Mitral stenosis. Auricular fibrillation. History of oedema.
17	60	35	Mitral and aortic incompetence. Auricular fibrillation.
87	76	36	Hyperpiesia. Arthritis of hip.
136	74	37	Hyperpiesia. Hemiplegia.

TABLE XIX

No.	Pulse.	Flush time.	Clinical condition.
		secs.	
122	84	31	Mitral stenosis and regurgitation. Paroxysm of auricular fibrillation. Liver tender. Six months pregnant.
90	136	32	Auricular flutter. Right bundle-branch block. Liver enlarged and tender. Orthopnoea.
119	80	33	Mitral stenosis and incompetence. Aortic incompetence. Auricular fibrillation. Liver palpable and tender.
156	68	33	Right bundle-branch block. Liver palpable.
40	88	34	Hyperpiesia. Liver enlarged and tender.
67	80	34	Hyperpiesia. Liver palpable. Previous oedema.
139	104	34	Hyperpiesia. Liver palpable and tender.
114	100	35	Mitral regurgitation. Liver palpable.
3	92	38	Aortic stenosis. Auricular fibrillation. Congested veins in the neck. Orthopnoea.
24	84	38	Mitral stenosis and incompetence. Aortic stenosis and incompetence. Auricular fibrillation. Liver large and pulsating.
106	44	39	Myocardial disease. Liver palpable.
37	—	40	Mitral regurgitation. Myocardial disease. Liver large. Recent oedema.

TABLE XX

No.	Pulse.	Flush time.	Clinical condition.
		secs.	
153	—	30	Mitral regurgitation. Portal cirrhosis.
8	90	35	Hyperpiesia. Eight months pregnant.
61	100	39	Auricular fibrillation. Varicose veins.
23	84	42	Mitral regurgitation. Myocardial disease.
85	90	42	Hyperpiesia. Large heart. Liver enlarged.
168	112	43	Hyperpiesia. Previous coronary thrombosis. Angina.
92	88	45	Mitral regurgitation. Angina.
46	64	45	Mitral and aortic stenosis and incompetence. Liver tender.
98	96	46	Hyperpiesia. Large heart. Liver large and tender.
149	88	48	Mitral regurgitation. Auricular fibrillation.
3	92	50	Aortic stenosis. Auricular fibrillation. Liver large. Orthopnoea.

TABLE XXI

No.	Flush time.	Clinical condition.
	secs.	
101	44	Previous coronary thrombosis. Right bundle-branch block. Chronic bronchitis. Orthopnoea. Great venous engorgement.
140	49	Right bundle-branch block. Auricular fibrillation. Pigmented.

TABLE XXII

No.	Flush time.	Clinical condition.
	secs.	
177	32	Angina. Mitral regurgitation. Intraventricular block.
91	35	Angina. Mitral regurgitation.
93	35	Angina. Mitral regurgitation.
175	38	Angina.
168	43	Angina. Hyperpiesia. Previous coronary thrombosis. Oedema.
92	45	Angina. Mitral regurgitation. Oedema.
140	49	Dyspnoea and tightness over chest. Auricular fibrillation. Right bundle-branch block.

TABLE XXIII

No.	Flush time.	Clinical condition.
	secs.	
176	32	Aortic regurgitation. Nocturnal attacks of dyspnoea for which he was kept in bed.
88	32	Right bundle-branch block. Auricular fibrillation. Under treatment for a month, in bed for the first fortnight.
144	34	Mitral stenosis. Auricular fibrillation. No exertion since an attack of jaundice a month previously.
21	35	Coronary thrombosis two months previously. No exertion allowed since.
80	36	Mitral stenosis and incompetence. In bed for two months following rheumatic fever three months previously, and still in one room.
46	37	Mitral and aortic stenosis and incompetence. Takes good care of himself. When this patient subsequently tried to return to work he developed oedema and a tender liver. (Table XX.)
132	39	Intracardiac thrombosis ten days previously. Absolute rest since.
131	39	Mitral regurgitation. Advanced osteo-arthritis of both knees.

TABLE XXIV

No.	Flush time.	Clinical condition.
	secs.	
8	35	Hyperpiesia. Oedema. Eight months pregnant.
137	37	Mitral regurgitation. This patient becomes very dyspnoeic on any exertion, and therefore does not do much.
61	39	Auricular fibrillation. Oedema. Varicose veins. This patient is very stout, and the liver would not be easy to feel.
95	40	Mitral regurgitation. Gallop rhythm. This patient is highly nervous, and the flush time may not be accurate.
23	42	Mitral regurgitation. Myocardial disease. Oedema.
149	48	Mitral regurgitation. Auricular fibrillation. Oedema.

TABLE XXV

No.	Pulse.	Flush time.	Clinical condition.
		secs.	
52	84	15	Landry's paralysis.
49	90	17	Congenital heart. Asthma.
78	—	18	Asthma.
104	100	19	Asthma.
145	90	19	Some emphysema.
169	72	20	Bronchiectasis.
151	80	22	Bronchitis. Substernal pain on exertion.
43	—	24	Mitral regurgitation. Chronic bronchitis and emphysema. Dyspnoea.
166	84	25	Asthma. Dyspnoea.
36	116	27	Pneumonia developing sudden dyspnoea and liver tenderness.
108	90	27	Hyperpiesia. Bronchitis. Liver enlarged and tender. Congestion of neck veins. Orthopnoea.
121	88	27	Hyperpiesia. Asthma. Orthopnoea. Previous oedema.
18	64	28	Cardiac pain. Emphysema.
53	—	29	Emphysema. Congested lung bases. Arthritis of hips.
82	108	29	Mitral regurgitation. Bronchitis. Dyspnoea.
101	124	29	Right bundle-branch block. Previous coronary thrombosis. Emphysema. Congestion of neck veins. Dyspnoea.
163	92	30	Old coronary thrombosis. Fibrosis of left lung. Liver enlarged and tender. Dyspnoea.

## THE PERIPHERAL CIRCULATION IN ACUTE LOBAR PNEUMONIA<sup>1</sup>

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ONE of the most serious groups of symptoms met with in lobar pneumonia is that indicative of circulatory failure. Such failure manifests itself by a persistently rapid heart-rate together with a fall in the systolic blood-pressure in the graver cases. Gibson (1) attempted to express this feature in his statement that if the blood-pressure in mm. of mercury fell below the pulse-rate the prognosis was very bad. Newburgh and Minot (2), however, found that it was not the fall in the blood-pressure that was of such grave importance, since in fatal cases the systolic pressure tended to be high, and that prognostic inferences based on Gibson's rule were wrong more often than right. They found that the rate of the pulse was the significant factor. Weigert (3) in a study of thirty-five cases came to much the same conclusion as regards the prognostic value of the blood-pressure in pneumonia. Edgeworth (4) has described a series of patients dying after the crisis in which death was always associated with a falling blood-pressure. Despite these different findings there can be little doubt that a large proportion of the patients in whom lobar pneumonia proves fatal die with symptoms of circulatory failure which, as Norris (5) pointed out, are closely similar to those seen in 'surgical shock'. Ritchie (6) has labelled this condition 'toxaemic shock' and states that although in pneumonia it is usually referred to as 'heart failure', he believes that it is more often the direct sequel of failure at the periphery of the circulation.

In an attempt to provide definite evidence of this a study of the behaviour of the small vessels of the skin in patients with lobar pneumonia has been made. Observations were made on the skin colour, the blood-pressure, the response of the skin vessels to histamine, to stroking, and to adrenalin, and finally the back pressure on the circulation required to obliterate the blanching produced by the latter. These observations were made as soon as possible after the patient's admission to hospital, and then repeated at intervals of three or four days throughout the course of the disease until discharge from hospital. At first these investigations were made every day, but as it was found that the changes in the various responses

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were taking place comparatively slowly, in the later cases they were repeated less frequently. Where possible the patients were re-examined at the end of convalescence. In all twenty-six cases of lobar pneumonia have been investigated in this way. A case of primary pleurisy (27) and a case of influenzal broncho-pneumonia (28) have been included in the case reports and are referred to for comparison with the other cases.

#### *Skin Colour*

The intensity of the skin colour on the flexor surface of the arm was noted according to the colour scale published by Lewis (7). This scale represents various depths of colour graded from the colour of the skin of the hand in extreme cyanosis and congestion (A) to the basal skin colour (K) of the bloodless hand, in a series of nine intermediate colours. Although Lewis states that the reproductions he published were not meant for use in practice, the difficulty of preparing an actual colour scale presented some difficulties to one whose 'eye for colour' is not too good, and it was found that in practice the actual skin colour could be matched in the reproduced scale with little difficulty. The various tints correspond with the amount of blood present in the skin and may be claimed to serve as a rough gauge of the degree of dilatation of the superficial blood-vessels of the skin.

The deepest colour noted was G in two of the three fatal cases (19 and 21) and in a fatal case of influenzal broncho-pneumonia (28) at the height of the disease. In the cases recovering the skin colour was H in seven cases before the crisis, in all of these the intensity decreased to I or J at the time, or shortly after, the temperature fell to normal. In the other cases the skin colour was I while the temperature was raised, lightening to J with the fall in the temperature. The colour I is not infrequently observed in normal persons and the significance of such a slight change is therefore difficult to assess. However, there would appear to be a definite tendency to a deepening in the intensity of the skin colour in lobar pneumonia, especially in the more severe cases, and a marked degree of such a change is of evil omen. The third fatal case (15) made a good recovery from the pneumonia but died of pneumococcal meningitis eight days after the crisis. The skin colour was J the day before death, although the temperature was 102° F. at the time. This would suggest that the intensity of the skin colour is not due to the rise of temperature.

#### *Blood-pressure*

In the majority of cases this was estimated with the Plesch Tonoscollograph, and in the remainder by the normal auscultatory method with an ordinary sphygmomanometer. Comparative readings with the recording 'Plesch' instrument and an ordinary sphygmomanometer showed that there was no appreciable difference in the systolic pressure as recorded with the two

methods. However, the diastolic pressure as measured with the recording apparatus tended to be about 5 mm. lower than when the normal auscultatory method was used. In the majority of the non-fatal cases the systolic pressure was higher before the crisis and fell immediately afterwards. The diastolic pressure was less affected by this change, so that the pulse-pressure also fell after the crisis. In six cases the crisis occurred shortly after admission to hospital and readings of the blood-pressure were not obtained until after the crisis. In the seventeen non-fatal cases in which comparable estimations were made the averages of the last observations made before the crisis and the first readings after the crisis are compared in Table I. This also shows the average of the last readings made before discharge from hospital. It is seen that during convalescence there was a tendency for both pressures to rise, but this rise was most marked in the diastolic pressure with a consequent fall in the pulse-pressure. The rather low diastolic pressures found may be due in part to the use of the tonoscillograph, but the same method was used in every reading in any one case, so that the figures are comparable. Case 7 illustrates this feature well.

*Case 7.* Samuel S. Aged 41. Two previous attacks of pneumonia. 14.11.31. Cold in head. 17.11.31. Pain in right side. Bloodstained sputum. 18.11.31. Delirious. 19.11.31. Admitted to hospital. Temperature 102.6. Pulse 80. Respirations 32. Rusty sputum. Diminished movement and impaired note at right base with bronchial breathing and pleural friction. 20.11.31. Blood-pressure 148/75. Skin colour H. Histamine puncture produced a well-marked wheal and flare. Stroking was followed by a fairly normal response. Adrenalin puncture resulted in a blanching of the skin which was obliterated by a back pressure of 40 mm. Hg. The blanching returned when the pressure was released. 22.11.31. Temperature fell by lysis to 90°. Pulse 83. Respirations 26. Post-critical rise the following day. 23.11.31. Blood-pressure 125/70. Skin colour J. Other skin reactions unaltered. 26.11.31. Blood-pressure 125/65. Skin colour J. Other skin reactions as before. 18.12.31. General condition improving rapidly. Blood-pressure 125/75. Skin colour J. Skin reactions as before, except that the adrenalin blanching withstood pressures up to 60 mm. Hg. 1.1.32. After fourteen days at convalescent home. Blood-pressure 130/80. Skin colour J. Adrenalin blanching now withstands a pressure of 80 mm. Hg.

TABLE I. *Showing the Average Blood-pressure in Seventeen Non-fatal Cases.*

	Systolic pressure in mm. of mercury.	Diastolic pressure in mm. of mercury.	Pulse pressure in mm. of mercury.
Before the crisis	128.1	65.2	62.9
After the crisis	117.6	65.1	52.5
At end of stay in hospital	117.9	66.8	51.1

In the three fatal cases the last readings before death were 130/70, 140/75. and 100/70 (Cases 15, 19, and 26 respectively).

*Response to Histamine*

A light prick was made into the skin of the flexor surface of the forearm through a drop of 1/6000 solution of histamine acid phosphate. In every case a central wheal developed in two minutes together with a surrounding flare, except that in those cases with a deep skin colour the flare was not very obvious. With this exception no appreciable difference in this reaction was noticed in the different stages of the disease or in different cases.

*Response to Stroking*

A fairly heavy stroke was made along the flexor surface of the forearm. One case (Case 3) whose arms were strongly tanned by exposure showed no response to stroking throughout the course of the disease. In sixteen of the non-fatal cases the response elicited was that described by Lewis (8) as the normal throughout the course of the disease, that is, a red line bounded at either side by a zone of blanching. In the remaining six non-fatal cases, before the crisis, and in two of the fatal cases (3, 10, 12, 14, 19, 20, 21, and 26) the red line appeared normally, but the white blanched border was poorly marked although only completely absent in one fatal case (19), and the case of influenzal broncho-pneumonia (28). This change from the normal response was most marked immediately before the crisis, or death, and the normal type of response returned fairly rapidly after the crisis. In the case dying of meningitis after the crisis (Case 15) the reaction to stroking was little altered from the normal.

*Response to Adrenalin*

The reaction of the small vessels of the skin to adrenalin was tested by making a light prick through a drop of 1/1000 adrenalin solution on the flexor surface of the forearm. In all cases, except one of the fatal cases (26), this produced a definite blanching of the skin in two minutes. This case (26) was examined about eighteen hours before death and no sign of blanching was seen. With a sphygmomanometer armlet on the arm the pressure was gradually raised, 10 mm. at a time, and each pressure was maintained for one minute. Lewis (8) has shown that in this way the pressure in the veins can be raised to, or to very slightly below, the pressure recorded by the manometer, presumably the same, or a slightly higher, pressure is present in the capillaries under such circumstances. In this way the back pressure required to obliterate the adrenalin blanching was ascertained. Lewis has shown that in normal subjects the small vessels contracted in response to adrenalin are able to resist distending pressures of as much as 80-100 mm. Hg. A preliminary study in ten normal students confirmed these findings. In twenty-five of the twenty-six cases of lobar

pneumonia adrenalin produced a satisfactory blanching, in twenty-one, however, this blanching was obliterated by congesting pressures of less than 70 mm. Hg. In Case 3, one day before the crisis (seventh day of the disease), the blanching was obliterated by only 30 mm. Hg. In Case 19 a similar response was found four days before death and this was unchanged the day before death when the patient was very toxic and delirious—that is, the adrenalin blanching was completely obliterated by a back pressure of 30 mm. Hg. In the case of influenzal broncho-pneumonia (28), the day before death, the blanching was completely obliterated by a back pressure of 20 mm. Hg. The ease with which the blanching could be obliterated increased until the crisis, after which the pressures required gradually rose until, in from 14–28 days time, the contracted vessels were able to withstand pressures of 80–100 mm. Hg. In some cases when recovery was complete the effect of the adrenalin could not be overcome with the patient's systolic pressure. In Case 22 the power of the adrenalin response to withstand back pressures fell for three days after the crisis and then gradually improved.

*Case 22.* Elsie P. Aged 49. 8.11.32. Rigor followed by pain in chest. 9.11.32. Admitted to hospital. Temperature 102.4°. Pulse 132. Respirations 28. Dullness at left base, bronchial breathing and increased vocal resonance. 11.11.32. Temperature 101°. Pulse 124. Respirations 30. Herpes labialis. Cyanosed. Troublesome cough. Blood-pressure 110/70. Skin colour H. Histamine puncture resulted in a well-marked wheal with a moderate surrounding flare. Stroking produced a red *tâche* bounded by white lines. Adrenalin puncture resulted in a blanched area which was obliterated by a back pressure of about 80 mm. Hg. Gradual fall of temperature to 98° on 12.11.32. Pulse 128. Respirations 30. Slight cyanosis persisted for two or three days. 15.11.32. Better, but lips still slightly cyanosed. Blood-pressure 95/70. Histamine stroking produced a normal response. Adrenalin blanching was obliterated by a pressure of 40 mm. Hg. 18.11.32. Steady improvement. Blood-pressure 105/68. Skin colour I. Adrenalin blanching very poor, obliterated by a pressure of 20 mm. Hg. Other skin reactions normal. 25.11.32. General condition much improved. Blood-pressure 110/68. Skin colour I. Adrenalin blanching withstands pressures up to 70 mm. Hg. Other skin reactions normal. 2.12.32. Getting up all day in the ward. Blood-pressure 120/72. Adrenalin blanching withstands pressures up to 110 mm. Hg. Other skin reactions normal.

In no case had the resistance of the contracted vessels returned to normal in less than fourteen days after the crisis. In three cases in which the symptoms were mild, and in the case dying of meningitis after the crisis the blanched skin withstood back pressures of over 80 mm. Hg. throughout the course of the disease (4, 6, 15, and 20). In a case of primary pleurisy (27) at the height of the disease the blanched area withstood back pressures up to the systolic pressure and could not be obliterated. This is in marked contrast to the cases with pneumonia, since in them the blanched areas did not withstand pressures over 100 mm. Hg. before the crisis. In one case (21) which developed an empyema this complication was without effect on the

recovery of the ability of the blanched skin to withstand distending pressures. In every case in which the blanching was obliterated by back pressure, the blanching returned on releasing the pressure.

The following case illustrates the varying response to adrenalin punctures throughout the course of the disease.

*Case 8.* Charles F. Aged 30. 1.12.31. General malaise and bad cough with rusty sputum. 3.12.31. Admitted to hospital. Skin flushed and sweating. Herpes labialis. Tongue furred and dry. Temperature 103.4. Pulse 120. Respirations 38. Diminished movement, impaired percussion note and bronchial breathing over the right base posteriorly. 4.12.31. Skin colour J. Blood-pressure 125/60. Histamine puncture produced a well-marked wheal and flare. Stroking was followed by a red line with a well-marked white border. Adrenalin puncture produced a fairly good blanching which was obliterated by a back pressure of 35 mm. of mercury, and returned after release of the pressure. 7.12.31. Condition much the same. Temperature 100.4. Pulse 100. Respirations 30. 8.12.31. Crisis. Temperature 98.4. Pulse 82. Respirations 28. Much better. Skin colour J. Blood-pressure 110/60. Response to histamine and stroking normal. Adrenalin produced a good blanching which was obliterated by a back pressure of 45 mm. of mercury. 10.12.31. Rapidly improving. Temperature 98.4. Pulse 82. Respirations 26. Skin colour J. Blood-pressure 110/55. Response to histamine and stroking normal. Adrenalin produced good blanching obliterated by a back pressure of 50 mm. of mercury. 16.12.31. Much better. Discharged to convalescent home. Skin colour J. Blood-pressure 110/55. Response to histamine and stroking normal. Adrenalin produced good blanching obliterated by a back pressure of 80 mm. of mercury. 1.1.32. After fourteen days at convalescent home. Greatly improved. Skin colour J. Blood-pressure 110/60. Response to histamine and stroking normal. Adrenalin produced good blanching which persisted despite the maximum back pressure that could be thrown on it.

Thus the cases may be divided roughly into four groups according to the reaction of the skin to adrenalin and the back pressure which the blanching so produced will withstand, at the height of the disease.

Group I. No response to adrenalin puncture. Case 26, a severely toxic case dying in eighteen hours.

Group II. Adrenalin produced blanching which was obliterated by a back pressure of 30 mm. Hg. or less, returning on release of pressure. Case 3, a very toxic case developing jaundice, presumably the result of the severe toxæmia. Case 19, a very toxic case, delirious for three days before death on the sixth day, and Cases 13 and 14. A case of influenzal broncho-pneumonia (28) also fell into this group.

Group III. In this group the adrenalin blanching at the height of the disease could be obliterated by pressures over 30 and below 70 mm. Hg. Seventeen cases (1, 2, 4, 5, 7, 8, 9, 10, 11, 12, 16, 17, 18, 21, 23, 24, and 25) of average severity fall into this group. Since all these cases improved during convalescence, and in all the ten normal controls the blanching withstood considerably higher pressures than these, it must be considered definitely abnormal.

Group IV. Those cases in which throughout the disease the blanching produced by adrenalin withstood back pressures of 80 mm. Hg. or over. Two mild cases (6 and 20) with fall of temperature on the 3rd and 4th day respectively fall into this group. Also the case of meningitis occurring after the crisis (15). This case was not observed before the onset of meningitis, eleven days after the onset. Case 22, which has already been described, and Case 18 appear to be anomalous in that the reaction to adrenalin depreciated after the crisis.

Thus a very close correlation was observed between the degree of toxæmia and the ease with which the area blanched by adrenalin could be obliterated by back pressures. The greater the toxæmia the less the back pressure required.

### *Discussion*

These findings support the view of Newburgh and Minot (2) that a fall in the blood-pressure is not the essential feature of the circulatory failure in lobar pneumonia. In experimental pneumonia, too, Newburgh and Porter (9) found that although there might be some slight fall in blood-pressure this was never so great as to endanger life until the actual point of death. The rise in the systolic pressure and pulse-pressure noted during the height of the disease may be compared with the observations of Bazett (10) who found that in surgical cases with acutely infected wounds there was almost constantly a rise in the systolic blood-pressure. This suggests that a rise in the systemic blood-pressure may be part of the usual mechanism for combating acute infections. The response of the vessels of the skin to stroking and to adrenalin would appear to indicate that the contractile power of the minute blood-vessels is definitely impaired in lobar pneumonia. Further, the recovery of these damaged vessels is slow and may be delayed for as long as a month after the crisis. It would appear that this impairment of the efficiency of the capillaries is due to some circulatory toxin. The increased intensity of the skin colour noted in the majority of the patients may be another manifestation of the same toxin producing a dilatation of the skin capillaries. The rapid return of the skin colour to normal after the crisis would appear to argue that the toxin production ceased with, or was efficiently neutralized after, the crisis. In which case the delayed recovery of the strength of the capillary reaction to adrenalin would be explained by the assumption that the damage to the capillaries persists after the removal of the toxin. A possible alternative to this explanation is that, although lessened after the crisis, the general intoxication in lobar pneumonia persists much longer than it is generally considered to do. The delay in the recovery is of further interest in that Maver and Schwartz (11) found that oedema (demonstrated by the elastometer) was present at the height of the disease in ten cases of lobar pneumonia in children and that this oedema disappeared very slowly during the convalescence. Harrison (12), also studying lobar pneumonia in children, reports the very rapid absorption of

intradermally injected salt solution. The crisis was without any immediate effect on this phenomenon, the return to normal being very slow, and even after five weeks the absorption was still more rapid than normal.

As long ago as 1899 Romberg (13) and his associates in an ingenious series of experiments claimed to have shown that in experimental infections with the pneumococcus (and other pathogenic organisms) there was no impairment of the myocardial efficiency, and that the circulatory failure observed was due to a poisoning of the vasomotor centres in the medulla. However, their positive results were only obtained constantly when the animal was practically on the point of death. Their conclusions have been criticized by Porter, Newburgh, and Newburgh (14) who repeated Romberg's experiments and found no evidence that the vasomotor centre was in any way affected in experimental pneumococcal infections. In a study of the myocardial efficiency in experimental cases Newburgh and Porter (15) demonstrated that if the heart of a normal animal was perfused with blood from an animal dying from pneumonia there was a marked impairment of the strength of the cardiac contractions when compared with those of a normal heart perfused with normal blood. However, when the hearts of animals dying from pneumonia were perfused with pneumonic blood they contracted practically as well as normal hearts perfused with normal blood. In addition the pneumonic hearts contracted less well when perfused with normal blood than when supplied with blood from animals with pneumonia. The conclusion drawn from these experiments is that the heart-muscle is not functionally impaired in pneumonia, and that it adapts itself very well to the altered toxic blood with which it is supplied. In acute myocardial failure one of the most constant and serious findings is a fall in the pulse-pressure. In pneumonia, however, as we have seen, there is rather a tendency to a rise in this pressure, and this is confirmed by experimental work (9).

From the histological point of view Thorel (16) states that the changes in the heart in pneumonia are not significant. Serious myocardial degenerations do not occur. Fatty degeneration is occasionally seen in older individuals. Romberg and his colleagues (13) found only slight changes in the heart-muscle, and similar findings have been reported by Aschoff and Tawara (17), Lubmann (18), and Eyslein (19). Stone (20), however, studied the hearts of thirty-four patients dying of lobar pneumonia and reports that in only 20.6 per cent. was the heart-muscle normal histologically. Parenchymatous degeneration was found in 52.9 per cent., 11.7 per cent. showed fatty degeneration and 2.9 per cent. hyaline changes. Infiltration with leucocytes and red blood cells occurred in 9.8 per cent., and a definite interstitial myocarditis was found in 2.9 per cent. It is difficult to explain such a high percentage of abnormal findings in view of the negative reports noted above. It is possible, however, that the parenchymatous degeneration noted in 52.9 per cent. of the cases was a slight change such as might be found in death associated with any fever.

In an electrocardiographic study of thirty-two cases of pneumonia receiving no digitalis, Arnett, and Harris (21) found what may be considered significant electrocardiographic abnormalities in four cases, while in only two cases were the tracings completely normal. The remainder showed slight changes of doubtful significance. De Graeff, Travell, and Yager (22) have also studied the electrocardiogram in lobar pneumonia and find that the pulse-rate is a valuable guide in prognosis, and that this varies little with the temperature. Conduction defects occurred in 10 per cent of the cases, and in 5 per cent. abnormalities of the basic rhythm were noted. Changes in the electrocardiogram developed at times after the temperature had returned to normal, and the authors conclude that the disease processes are active in the heart even after the crisis. Levy (23) studied the size of the heart by X-rays in twenty-one cases of lobar pneumonia and found that cardiac dilatation occurred in 61.9 per cent. He suggests that these findings may be explained, apart from structural changes in the heart muscle, by an increased strain thrown on the heart either by the impaired circulation in the affected lung, by toxæmia or by anoxæmia. Kastlin and MacLachlan (24) investigated the venous pressure in a total of ninety cases of lobar pneumonia. The venous pressure was definitely high in thirty-four cases, twenty-four of which died. Of the thirty-seven cases with venous pressures within normal limits throughout the illness only five died. They conclude that an increase of the venous pressure is of value in lobar pneumonia in aiding the recognition of circulatory failure, and that the degree of this failure is best estimated by a correlation of the venous pressure and the pulse-rate.

Thus both experimental and clinical observations suggest that in the majority of cases of lobar pneumonia both the vasomotor centre and the myocardium suffer little damage, and yet the patient dies of circulatory failure. The findings reported in this paper, offer considerable support to Ritchie's suggestion (6) that the circulatory failure in lobar pneumonia is really a failure of the circulation at the periphery; and they help to reconcile the various experimental findings. If this theory be accepted it has obvious bearings on the appropriate treatment to be adopted, since efforts to stimulate, and improve the tone of the minute blood-vessels are more likely to benefit the patient than attempts to increase the efficiency of the heart itself. The slow recovery in the behaviour of the capillaries observed in this study indicates the need for prolonged and careful convalescence in lobar pneumonia.

#### *Summary and Conclusion*

1. The reactions of the small vessels of the skin have been studied in twenty-six cases of lobar pneumonia.
2. These reactions show an impaired efficiency in the contractility of the capillaries at the height of the disease.

3. The recovery of the capillaries is slow and not immediately affected by the crisis.

4. Part, at least, of the circulatory failure met with in lobar pneumonia is due to this impaired efficiency of the small blood-vessels.

5. The blood-pressure is raised rather than lowered during the acute phase of the disease.

My thanks are due to those physicians of the Bristol General Hospital and Bristol Royal Infirmary who kindly gave me permission to examine their patients. The work has been done under the tenure of a Beaverbrook Research Fellowship.

#### *Case Reports*

*Case 1.* Ernest P. Aged 14. 29.7.31. Sudden onset of abdominal pain with fever. 30.7.31. Pain in the left side. 31.7.31. Delirious. 1.8.31. Admitted to hospital. Temperature 103.2°. Pulse 140. Respirations 32. Dullness at right base with diminished movement. 2.8.31. Crisis. Temperature 97°. Pulse 88. Respirations 20. Uncomplicated recovery. 5.8.31. Blood-pressure 120/80. Skin colour I. Histamine puncture gave a normal wheal and flare. Stroking the skin produced a normal response. Adrenalin puncture produced a blanching which was obliterated with a back pressure of 50 mm. Hg. 7.8.31. Blood-pressure 100/60. Skin colour I. Normal responses to histamine puncture and stroking. Adrenalin puncture produced a blanching obliterated by a back pressure of 60 mm. Hg. 13.8.31. Blood-pressure 100/60. Skin colour I. Normal responses to histamine puncture and stroking. Adrenalin blanching obliterated by a back pressure of 70 mm. Hg. 15.viii.31. Discharged to convalescent home. 21.viii.31. Blood-pressure 110/65. Skin colour J. Normal responses to stroking and histamine puncture. Adrenalin blanching obliterated by a back pressure of 90 mm. Hg.

*Case 2.* Gilbert G. Aged 28. 19.9.31. Rigor with pain in left chest. 20.9.31. Delirious. 21.9.31. Small haemoptysis. 22.9.31. Admitted to hospital. Very flushed and sweating. Temperature 102.8°. Pulse 100. Respirations 36. Impaired percussion note at both bases posteriorly. Breath sounds diminished and bronchial in character at both bases. Fine râles at right base. 23.9.31. Skin colour I. Blood-pressure 130/65. Histamine puncture produced a normal wheal and flare. Stroking the skin produced a red line with little or no blanching at the edges. Adrenalin blanching was obliterated by a back pressure of 40 mm. Hg. 24.9.31. Skin colour K. Blood-pressure 130/70. Stroking the skin produced a red line with no peripheral blanching. Other responses unchanged. 25.9.31. Skin colour J. Blood-pressure 150/65. Response to histamine puncture normal. Stroking produced a red line with a very slight peripheral blanching. Adrenalin blanching obliterated by a back pressure of 30 mm. Hg. 27.9.31. Temperature 102.6°. Pulse 104. Respirations 68. 28.9.31. Temperature fell by crisis to 97.8°. Respirations 44. Pulse 104. Much better. Skin colour J. Blood pressure 140/65. Histamine and stroking produced normal responses. Adrenalin blanching obliterated by back pressure of 30 mm. Hg. 1.10.31. Skin colour J. Blood-pressure 150/70. Response to histamine

puncture and to stroking normal. Adrenalin blanching obliterated at a back pressure of 40 mm. Hg. 6.10.31. Skin colour J. Blood-pressure 130/60. Responses to histamine puncture and to stroking normal. Adrenalin blanching obliterated by a back pressure of 40 mm. Hg. 7.10.31. Temperature had remained normal. Uncomplicated recovery. Skin colour J. Blood-pressure 145/65. Responses to histamine puncture and to stroking normal. Adrenalin blanching obliterated by pressure of 60 mm. Hg. 16.10.31. At convalescent home. Skin colour J. Blood-pressure 140/75. Response to histamine puncture and stroking normal. Adrenalin blanching obliterated by 70 mm. Hg. back pressure. 28.10.31. Skin colour J. Blood-pressure 120/75. Responses to histamine puncture and stroking normal. Adrenalin blanching could not be obliterated by systolic pressure (120 mm. Hg.).

*Case 3.* Leonard D. Aged 34. N.B.—This patient's arms were very much tanned from exposure which made the readings very difficult. 9.10.31. Pain in the right side with worrying cough and fever. 16.10.31. Admitted to hospital. Temperature 101.8°. Pulse 108. Respirations 48. Slight jaundice. Impaired percussion note with bronchial breathing at the right base. Skin colour I. Blood pressure 135/60. Stroking produced a red line with no blanching at the edges. Histamine puncture produced a wheal but no obvious flare. Adrenalin blanching obliterated by a back pressure between 20 and 30 mm. Hg. Gradual fall of temperature to 98° on 19.10.31. Pulse 76. Respirations 30. Uncomplicated recovery with rapid fading of jaundice. 20.10.31. Skin colour J. Blood-pressure 120/60. Stroking produced a poor indefinite response. Histamine puncture produced a wheal with an indefinite flare. Adrenalin blanching obliterated by pressure of 30 mm. Hg. 23.10.31. Skin colour J. Blood-pressure 125/55. Histamine puncture resulted in a wheal with a slight flare. Stroking produced very little response. Adrenalin blanching obliterated by pressure of forty mm. Hg. 26.10.31. Skin colour J. Blood-pressure 125/55. Response to histamine puncture and to stroking unchanged. Adrenalin blanching obliterated by back pressure of 40 mm. Hg. 30.10.31. Skin colour J. Blood-pressure 120/55. Response to histamine puncture and stroking unchanged. Adrenalin blanching obliterated by 50 mm. Hg. back pressure. 3.11.31. Skin colour J. Blood-pressure 125/60. Response to histamine puncture and stroking unchanged. Adrenalin blanching obliterated by back pressure of 60 mm. Hg. 13.11.31. Skin colour J. Blood-pressure 140/70. Response to histamine puncture and stroking unchanged. Adrenalin blanching obliterated by back pressure of 70 mm. Hg. 27.11.31. Skin colour J. Blood-pressure 130/70. Response to histamine puncture and stroking unchanged. Adrenalin blanching obliterated by back pressure of 70 mm. Hg.

*Case 4.* Albert W. Aged 27. 30.10.31. Pain in the side with cough and rusty sputum. 1.11.31. Admitted to hospital. Temperature 102.4°. Pulse 120. Respirations 40. Impaired movement and percussion note at right base with bronchial breathing. 2.11.31. Skin colour I. Blood-pressure 130/65. Histamine puncture gave a normal wheal with a slight or absent flare. Stroking produced a normal response. Adrenalin blanching obliterated by 60 mm. Hg. back pressure. 4.11.31. Crisis. Temperature 98°. Pulse 90. Respirations 38. Uncomplicated recovery, except that on discharge 20.11.31. there was still diminished expansion and air entry at the right base. 5.11.31. Skin colour I. Blood-pressure 120/70. Response to histamine and to stroking unchanged. Adrenalin blanching obliterated

by pressure of 80 mm. Hg. 10.11.31. Skin colour J. Blood-pressure 125/70. Histamine puncture produced a normal wheal and flare. Stroking produced a normal response. Adrenalin blanching obliterated by pressure of 80 mm. Hg. 4.12.31. Skin colour I. Blood-pressure 125/80. All responses unchanged. 18.12.31. Skin colour I. Blood-pressure 120/80. Histamine puncture and stroking produced normal responses. Adrenalin blanching obliterated by 100 mm. Hg. back pressure.

*Case 5.* Ellen D. Aged 29. Chronic rheumatic heart disease with mitral stenosis. Four previous attacks of pneumonia. 31.10.31. Admitted to hospital on the fourth day of the illness. Temperature 103.2°. Pulse 116. Respirations 60. Impaired movement and dullness at right base with bronchial breathing. 1.11.31. Temperature fell by lysis to 98.4°. Pulse 96. Respirations 48. Prolonged but uncomplicated recovery. On discharge, chest normal except for inspiratory râles at right base. 2.11.31. Skin colour I. Blood-pressure 105/65. Histamine puncture and stroking produced normal responses. Adrenalin blanching obliterated by 60 mm. Hg. back pressure. 5.11.31. Skin colour J. Blood-pressure 110/65. All responses unchanged. 10.11.31. Skin colour J. Blood-pressure 85/55. All responses unchanged. 17.11.31. Skin colour J. Blood-pressure 90/60. Histamine puncture and stroking produced normal responses. Adrenalin blanching obliterated by back pressure of 80 mm. Hg. 20.11.31. Skin colour I with a tendency to cyanosis. Blood-pressure 90/55. Response to histamine puncture and to stroking normal. Adrenalin blanching obliterated by back pressure of 70 mm. Hg. 26.11.31. Skin colour J. Blood-pressure 100/55. Response to histamine puncture and to stroking normal. Adrenalin blanching obliterated by back pressure of 80 mm. Hg. 4.12.31. Skin colour I. Blood-pressure 95/55. Response to histamine puncture and to stroking normal. Adrenalin blanching obliterated by 90 mm. Hg. back pressure.

*Case 6.* Elver C. Aged 16. 13.11.31. Woke with sharp pain in chest and slight haemoptysis. 14.11.31. Admitted to hospital. Temperature 104°. Pulse 120. Respirations 40. Impaired note at right base with râles. Herpes labialis. 16.11.31. Temperature fell by lysis to 97°. Pulse 84. Respirations 22. Uncomplicated recovery. 19.11.31. Skin colour I. Blood-pressure 95/60. Normal responses to histamine puncture and to stroking. Adrenalin blanching could not be obliterated by systolic pressure. 23.11.31. Skin colour K. Blood-pressure 105/55. Responses to histamine puncture and to stroking unaltered. Adrenalin blanching obliterated by 90 mm. Hg. 26.11.31. Discharged to convalescent home. 11.12.21. Skin colour J. Blood-pressure 105/55. Normal responses to histamine puncture and to stroking. Adrenalin blanching could not be obliterated.

*Cases 7 and 8* described in full in the text.

*Case 9.* Samuel H. Aged 36. 26.12.31. Rigor following 2 weeks cold and cough. Troublesome cough with pink sputum. 30.12.31. Admitted to hospital. Temperature 103°. Pulse 110. Respirations 32. Impaired percussion note at right base with fine râles. 31.12.31. Skin colour J. Blood-pressure 120/60. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated at 50 mm. Hg. back pressure. 1.1.32. Crisis. Temperature 98°. Pulse 84. Respirations 26. Recovery complicated by mild tonsillitis on 12.1.32. 4.1.32. Skin colour K. Blood-pressure 115/65. Responses to histamine puncture and to stroking normal.

Adrenalin blanching obliterated by 60 mm. Hg. back pressure. 7.1.32. Skin colour K. Blood-pressure 130/60. Responses to histamine puncture and to stroking normal. Adrenalin blanching obliterated by 70 mm. Hg. back pressure. 12.1.32. Skin colour K. Blood-pressure 120/50. Responses to histamine puncture and to stroking normal. Adrenalin blanching obliterated by 80 mm. Hg. back pressure. 25.1.32. Skin colour J. Blood-pressure 110/65. Responses to histamine puncture and to stroking normal. Adrenalin blanching obliterated by 100 mm. Hg. back pressure.

*Case 10.* George B. Aged 42. 27.12.31. Pain in the right side with a shivering attack. This followed an indefinite febrile illness of about seven days duration. 28.12.31. Admitted to hospital. Temperature 102.8°. Pulse 84. Respirations 40. Diminished movement and air entry at right base. No further physical signs developed. Skin colour J. Blood pressure 115/60. Histamine puncture resulted in a well-marked wheal with a poor flare. Stroking produced a red line with faintly blanched borders. Adrenalin blanching obliterated by 80 mm. Hg. back pressure. Temperature fell gradually to 98° on 31.12.31. Pulse 78. Respirations 22. Uncomplicated and rapid recovery. Skin colour J. Blood-pressure 105/55. Histamine puncture resulted in a well-marked wheal with a poor flare. Stroking produced a red line with faintly blanched borders. Adrenalin blanching obliterated by 80 mm. Hg. back pressure. 4.1.32. Skin colour J. Blood-pressure 120/60. Responses to histamine puncture and to stroking normal. Adrenalin blanching could not be obliterated. 7.1.32. Skin colour I. Blood-pressure 120/55. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 100 mm. Hg. back pressure. 29.1.32. Skin colour I-J. Blood-pressure 110/65. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 90 mm. Hg. back pressure.

*Case 11.* Maud C. Aged 35. 4.1.32. Rigor followed by cough and pain in right side. 6.1.32. Admitted to hospital. Temperature 101.2°. Pulse 112. Respirations 32. Herpes labialis. Dullness at right base with bronchial breathing. 8.1.32. Skin colour J. Blood-pressure 115/65. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 80 mm. Hg. back pressure. 10.1.32. Temperature 103.8°. Pulse 108. Respirations 36. Temperature fell by lysis to 99°. Pulse 84. Respirations 24. Uncomplicated recovery. 11.1.32. Skin colour J. Blood-pressure 115/65. Histamine puncture produced a good wheal with a poor flare. Stroking produced a red line with faintly blanched borders. Adrenalin blanching obliterated by 50 mm. Hg. back pressure. 15.1.32. Skin colour J. Blood-pressure 115/65. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 70 mm. Hg. back pressure. 18.1.32. Skin colour J. Blood-pressure 115/60. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 90 mm. Hg. back pressure. 23.1.32. Skin colour J. Blood-pressure 110/65. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 100 mm. Hg. back pressure.

*Case 12.* Leonard B. Aged 19. Attack of 'flu' with good recovery and return to work for three days. 20.2.32. Woke with pain in chest and cough. 24.2.32. Admitted to hospital. Slightly cyanosed. Temperature 103.4°. Pulse 108. Respirations 36. Rusty sputum. Impaired percussion note at right base. 25.2.32. Skin colour I. Blood-pressure 115/55. Normal response to histamine puncture. Stroking produced a well-

marked red line with rather poorly blanched borders. Adrenalin blanching obliterated by 60 mm. Hg. back pressure. Gradual fall of temperature to 97° on 28.2.32. Pulse 92. Respirations 26. Uncomplicated recovery. 29.2.32. Skin colour J. Blood-pressure 120/65. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 110 mm. Hg. back pressure. 4.3.32. Skin colour J. Blood-pressure 115/60. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 70 mm. Hg. back pressure.

*Case 13.* Betty H. Aged 18. 28.2.32. Shivering attack. Severe pain in left side. Irritating cough. Two previous attacks of pneumonia. 2.3.32. Admitted to hospital. Temperature 104°. Pulse 128. Respirations 32. 3.3.32. Skin colour J. Blood-pressure 110/70. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 30 mm. Hg. back pressure. 4.3.32. Pain very severe and exhausting. Temperature 101.2°. Pulse 108. Respirations 36. Skin colour I-J. Blood-pressure 100/65. Normal response to histamine puncture. Stroking produced a red line with poorly blanched borders. Adrenalin blanching obliterated by 30 mm. Hg. back pressure. 6.3.32. Crisis, uncomplicated recovery.

*Case 14.* Ethel O. Aged 42. 20.3.32. Admitted to hospital. Cough with pain in left side for about a week. Temperature 102°. Pulse 120. Respirations 36. 25.3.32. Crisis. Temperature 98°. Pulse 84. Respirations 24. 1.4.32. Temperature 103°. Pulse 120. Respirations 40. Dullness with bronchial breathing left base. Aegophony at the upper limit of dullness. Area of dullness and bronchial breathing at right base. 4.4.32. Temperature fell to 99°. Pulse 96. Respirations 24. 5.4.32. Skin colour J. Blood-pressure 130/75. Normal response to histamine puncture. Stroking produced a red line with faintly blanched borders. Adrenalin blanching obliterated by 30 mm. Hg. back pressure. 8.4.32. Temperature had been rather swinging. 100 c.c. of clear yellow fluid aspirated from left chest. (Cells 78 per cent. lymphocytes). Skin colour J. Blood-pressure 120/80. Normal response to histamine puncture. Stroking produced a red line with faintly blanched borders. Adrenalin blanching obliterated by 40 mm. Hg. back pressure. 12.4.32. Temperature 98°. Pulse 112. Respirations 24. Skin colour J. Blood-pressure 115/75. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 70 mm. Hg. back pressure. 15.4.32. Skin colour J. Blood-pressure 100/70. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 70 mm. Hg. back pressure. 16.4.32. Temperature 97.8°. Pulse 72. Respirations 24. X-ray shows some fluid at the left base and on the right side a dull area in the middle of the chest. ? Interlobar fluid. ? Consolidation. No further rise of temperature. Good recovery. 21.4.32. Skin colour J. Blood-pressure 115/80. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 90-100 mm. Hg. back pressure.

*Case 15.* Lilian T. Aged 23. 26.3.32. Admitted to hospital on third day of illness. Temperature 101.2°. Pulse 120. Respirations 36. Skin flushed and sweating. Pain in left chest. Diminished movement, impaired percussion note and bronchial breathing at left base. 30.3.32. Temperature fell by lysis to 98°. Pulse 100. Respirations 36. Continued to improve until 3.4.32. when temperature rose to 102.4°. Respirations 40. Pulse 132.

The next day meningeal signs developed. 4.4.32. Skin colour J. Blood-pressure 125/79. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 100 mm. Hg. back pressure. 5.4.32. Lumbar puncture showed purulent C.S.F. containing pneumococci. 7.4.32. Skin colour J. Blood-pressure 130/70. All skin reactions as on 4.4.32. Unconscious, restless with marked head retraction. Died some hours later.

*Case 16.* William S. Aged 46. 30.3.32. Pain in left side. Cough with bloodstained sputum. 1.4.32. Admitted to hospital. Temperature 102.6°. Pulse 120. Respirations 28. Dullness at the left base with bronchial breathing. Crepitations at right base. 5.4.32. Crisis. Temperature 98. Pulse 108. Respirations 32. Uncomplicated recovery. 6.4.32. Skin colour J. Blood-pressure 95/60. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 60 mm. Hg. back pressure. 8.4.32. Skin colour J. Blood-pressure 100/55. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 70 mm. Hg. back pressure. 12.4.32. Skin colour K. Blood-pressure 105/55. Normal responses to histamine puncture and to stroking. Adrenalin blanching was poorly marked and obliterated by 50 mm. Hg. back pressure. This was probably due to deterioration of the adrenalin solution. This was found to occur frequently and necessitated the use of fresh solutions. 15.4.32. Skin colour J. Blood-pressure 100/60. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 90 mm. Hg. back pressure. 21.4.32. Skin colour J. Blood-pressure 105/65. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 100 mm. Hg. back pressure.

*Case 17.* Arthur L. Aged 41. 28.4.32. Rigor with pain on breathing and a slight cough. 30.4.32. Admitted to hospital. Temperature 104.5°. Pulse 110. Respirations 32. Bloodstained sputum. Impaired movement and dullness to percussion at right base with bronchial breathing. 3.5.32. Skin colour H. Blood-pressure 110/60. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 50 mm. Hg. back pressure. 6.5.32. Colour H. Blood-pressure 115/60. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 60 mm. Hg. back pressure. 7.5.32. Crisis. Temperature 98.6°. Pulse 100. Respirations 40. Uncomplicated recovery. 9.5.32. Skin colour I. Blood-pressure 115/65. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 50 mm. Hg. back pressure. 13.5.32. Skin colour I. Blood-pressure 120/70. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 80 mm. Hg. back pressure.

*Case 18.* James D. Aged 43. 3.8.32. Sudden pain in both chests. Collapsed at work with a rigor. 4.8.32. Admitted to hospital. Temperature 104°. Pulse 104. Respirations 30. 5.8.32. Herpes labialis. Cyanosed. Alae nasi working. Impaired percussion note over both bases with fine râles and increased vocal resonance. 6.8.32. Crisis. Temperature 98°. Pulse 92. Respirations 30. 7.8.32. Post-critical rise of temperature to 100.6°. Pulse 80. Respirations 20. Uncomplicated recovery. 8.8.32. Skin colour H. Blood-pressure 140/90. Normal responses to histamine puncture and to stroking. Adrenalin blanching could not be obliterated. 12.8.32. Skin colour I. Blood-pressure 120/75. Normal

responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 110 mm. Hg. back pressure. 16.8.32. Skin colour I. Blood-pressure 115/75. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 80 mm. Hg. back pressure. 19.8.32. Skin colour H. Blood-pressure 125/70. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 60 mm. Hg. back pressure.

(The two last observations were made in a sweltering heat and on both occasions the patient was perspiring profusely, this may in part account for the anomalous results).

*Case 19.* Francis C. Aged 43. 18.8.32. Rigor with sudden onset of pain in the left chest. 19.8.32. Admitted to hospital. Flushed and cyanosed. Perspiring freely. Temperature 102°. Pulse 104. Respirations 36. Diminished movement of the left base with inspiratory recession of the intercostal spaces. Impaired percussion note over the left base posteriorly, with bronchial breathing. Skin colour G-H. Blood-pressure 150/70. Histamine puncture produced a wheal with a very poor surrounding flare. Stroking produced a normal response. Adrenalin blanching obliterated by 40 mm. Hg. back pressure. 22.8.32. Temperature 100°. Pulse 130. Respirations 40. Increasing delirium. Skin colour H. Blood-pressure 140/75. Histamine puncture produced a wheal with no definite flare. Stroking produced a red line with very slight blanching at the borders. Adrenalin blanching obliterated by 30 mm. Hg. back pressure. 23.8.32. Very delirious and restless. Skin colour H. Stroking produced a red line with very faint blanching at the borders. The patient was too restless for other observations to be made. 24.8.32. Temperature 103°. Pulse 160. Respirations 64. Death. *Post mortem* showed acute lobar pneumonia of the bases of both lungs.

*Case 20.* Harold H. Aged 16. 29.8.32. Rigor followed by fever, headache, severe pain in chest and slight cough. 1.9.32. Admitted to hospital. Temperature 102°. Pulse 100. Respirations 38. Impaired note with bronchial breathing and increased vocal resonance at left base. 3.9.32. Herpes labialis. Skin colour H-I. Blood-pressure 115/60. Normal response to histamine puncture. Stroking produced a red line with poor blanching at the borders. Adrenalin blanching obliterated by 100 mm. Hg. back pressure. 5.9.32. Crisis. Temperature 98°. Pulse 80. Respirations 22. 6.9.32. Temperature 100.4°. Gradual fall to normal. Otherwise uncomplicated recovery. 12.9.32. Skin colour I. Blood-pressure 120/80. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 90 mm. Hg. back pressure. 16.9.32. No abnormal physical signs except for fine inspiratory râles at left base. 20.9.32. Skin colour I. Blood-pressure 120/50. Normal responses to histamine puncture and to stroking. Adrenalin puncture obliterated by 110 mm. Hg. back pressure.

*Case 21.* Frederick B. Aged 22. 2.11.32. He complained of 'a cold in the head'. Was at work normally until 9.11.32, when he developed a pain in the chest, with slight cough and he was feverish. 14.11.32. Admitted to hospital. Face flushed. Respirations rapid and shallow (40 a minute). Temperature 100.5°. Pulse 96. Sputum rusty. Poor expansion of the lower part of the chest on both sides with impaired percussion note and diminished breath sounds, bronchial in character. Pleural friction

heard at both bases. 18.11.32. Condition little changed. Temperature 98°. Pulse 76. Respirations 26. Skin colour H. Blood-pressure 125/60. Normal response to histamine puncture. Stroking produced a red line with faintly blanched borders. Adrenalin blanching obliterated by 50 mm. Hg. back pressure. 19.11.32. Crisis. Condition much improved. Temperature 98°. Pulse 76. Respirations 26. 23.11.32. Temperature 99°. Pulse 76. Respirations 20. Physical signs: right chest clearing but left base absolutely dull to percussion with absent breath sounds. 24.11.32. Left chest explored. Pus found. Culture showed a pure growth of pneumococci. Rib resected and pleura drained. 25.11.32. Skin colour H-I. Blood-pressure 125/60. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 60 mm. Hg. back pressure. 1.12.32. Gradually improving. Chest still draining well. Skin colour I. Blood-pressure 125/60. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 80 mm. Hg. back pressure. 9.12.32. Temperature rose to 99.8° and pus was found to be pocketing in the pleura. Drainage improved. Slight discharge from the sinus persisted until 16.12.32. 16.12.32. Skin colour J. Blood-pressure 115/55. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 90 mm. Hg. back pressure. 22.12.32. Greatly improved. Skin colour I. Blood-pressure 115/58. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 100 mm. Hg. back pressure. 5.1.33. Skin colour I. Blood-pressure 105/55. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 100 mm. Hg. back pressure.

*Case 22* described in full in the text.

*Case 23.* Albert B. Aged 29. 27.11.32. Rigor. 29.11.32. Pain in right side. 1.12.32. Admitted to hospital. Temperature 102.6°. Pulse 110. Respirations 46. Diminished movement with increased vocal fremitus. Impaired percussion note with increased vocal resonance and coarse râles. (? pleural friction) at right base. Skin colour H. Blood-pressure 140/70. Histamine puncture produced a wheal but the flare was rather obscured by the deep skin colour. Stroking resulted in a red line with slight blanching at the edges. Adrenalin blanching obliterated by 60 mm. Hg. back pressure. 6.12.32. Crisis. Temperature 98°. Pulse 86. Respirations 30. Good progress until 12.12.32. when temperature rose to 100.8° and developed a swinging character. Increased dullness at right base with diminished breath sounds. Skin colour H. Blood-pressure 110/70. Histamine puncture resulted in a wheal with an ill-defined flare (? due to deep skin colour). Stroking produced a red line with slightly blanched edges. Adrenalin blanching obliterated by 70 mm. Hg. back pressure. 14.12.32. Sputum showed no tubercle bacilli. 15.12.32. Chest needled. No fluid found. Irregular fever continued until 26.12.32. The physical signs in the lungs showed little change except that medium râles were occasionally heard over the dull area. Gradual recovery took place with no further fever until discharge 14.2.33. when percussion note was still poor at right base. 16.12.32. Skin colour I. Blood-pressure 118/60. Normal response to histamine puncture. Response to stroking as on 6.12.32. Adrenalin blanching obliterated by 60 mm. Hg. back pressure. 22.12.32. Skin colour I. Blood-pressure 105/60. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 70 mm. Hg. back pressure. 5.1.33. Skin colour I. Blood-pressure 115/55. Normal responses to histamine

puncture and to stroking. Adrenalin blanching obliterated by 70 mm. Hg. back pressure.

*Case 24.* Dorothy B. Aged 31. 29.11.32. Pain in left side. Cough with bloodstained sputum. 4.12.32. Admitted to hospital. Temperature 101°. Pulse 120. Respirations 52. Dullness at left base with bronchial breathing and fine râles. Crisis. Temperature falling to 99°. 6.12.32. Temperature rose to 100°. Pulse 116. Respirations 32. Temperature fell to 94° in twelve hours. Skin colour J. Blood-pressure 120/70. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 50 mm. Hg. back pressure. 8.12.32. Another rise of temperature to 100°. Pulse 100. Respirations 26. 9.12.32. Skin colour I. Blood-pressure 125/72. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 70 mm. Hg. back pressure. 10.12.32. Temperature 97.8°. Pulse 96. Respirations 24. Uneventful recovery. 16.12.32. Skin colour I. Blood-pressure 110/68. Normal responses obliterated by 80 mm. Hg. back pressure. 22.12.32. Skin colour I. Blood-pressure 100/60. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 90 mm. Hg. back pressure.

*Case 25.* Minnie S. Aged 48. Cold and cough for some time. 19.12.32. Pain in left side. 20.12.32. Bloodstained sputum. Admitted to hospital. Temperature 99°. Pulse 126. Respirations 40. 22.12.32. Temperature 100°. Pulse 120. Respirations 34. Impaired note at the left base with bronchial breathing. Skin colour I. Blood-pressure 120/70. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 60 mm. Hg. back pressure. 24.12.32. Temperature fell to 98°. Pulse 90. Respirations 24. 27.12.32. Herpes labialis. Slow but uncomplicated recovery. Skin colour I. Blood-pressure 130/75. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 70-80 mm. Hg. back pressure. 30.12.32. Skin colour H. Blood-pressure 130/80. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 70 mm. Hg. back pressure. 5.1.33. Skin colour I. Blood-pressure 140/80. Normal responses to histamine puncture and to stroking. Adrenalin blanching obliterated by 100 mm. Hg. back pressure.

*Case 26.* William G. Aged 39. 22.12.32. Sudden rigor while at work. This was followed by general malaise and weakness. Slight cough and pain in the left chest. 23.12.32. Admitted to hospital. Temperature 103°. Pulse 112. Respirations 24. Flushed and sweating, with grunting respirations. Impaired movement and percussion note over the base of the left lung with bronchial breathing. 25.12.32. General condition much worse. Temperature 104.2°. Pulse 130. Respirations 40. Rather cyanosed. Restless and delirious at times. 26.12.32. Much worse. Marked cyanosis, slightly relieved by oxygen. Unconsciousness alternating with delirium. Temperature 104.6°. Pulse 140. Respirations 48. Skin colour G-H. Blood-pressure 100/70. Normal response to histamine puncture. Stroking produced a red line with no blanching at the borders. Adrenalin puncture produced no blanching. Death six hours later. *Post mortem* showed fibrinous pleurisy over the left lobe which was in a condition of gray hepatisation with early purulent infiltration. Acute congestion of the right lower lobe with early pleurisy.

*Case 27.* Agnes S. Aged 18. 1.3.32. Rigor and pain in the chest. 2.3.32. Admitted to hospital. Looks fairly well. Complains of pain in left chest on inspiration. Temperature 102.4°. Pulse 120. Respirations 40. Diminished movement of left base with marked pleural friction rub. Skin colour J. Blood-pressure 105/65. Normal responses to histamine puncture and to stroking. Adrenalin blanching cannot be obliterated by back pressures up to the systolic pressure. 3.3.32. Temperature 97.6°. Pulse 92. Respirations 20. Pain gone. Much better. Rapid convalescence.

This case has not been included in the series but is described here to show the difference in the findings from those met with in a true lobar pneumonia.

*Case 28.* Phyllis P. Aged 18. Not included in the series. 22.2.32. Sore throat. 23.2.32. Severely ill with high temperature, and pain in side, and cough. 24.2.32. Admitted to hospital. Temperature 105°. Pulse 170. Respirations 48. 25.2.32. Skin colour G. Blood-pressure difficult to estimate because of poor pulse. Histamine puncture produced a wheal with no flare. Stroking produced a red line with no blanching at the borders. Adrenalin blanching obliterated at 20 mm. Hg. back pressure. Death in two hours. *Post mortem.* Acute influenzal broncho-pneumonia.

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CALCINOSIS<sup>1</sup>

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With Plates 18 and 19

*Introduction*

As long ago as 1878 Weber (78), reported a case in which subcutaneous and cutaneous calcareous deposits occurred in association with sclerodactylia. Since then more than 120 cases of the condition, which he was the first to describe, and which we now know as calcosinosis, many of them exhibiting the same or an allied association of diseases, have appeared in medical literature; and, no doubt, many others have been diagnosed and studied though not reported. The disease, therefore, although relatively rare, would now appear to be well recognized as a distinct pathological entity, and in view of the considerable advances during the last fifty years in almost every aspect of medical investigation and therapy, it might be expected that much more positive knowledge of this condition would have been accumulated. In point of fact the position to-day remains very much as Weber left it fifty-five years ago.

The major advances in our knowledge, both of calcium metabolism and of pathological calcification in man, are, however, recent; and it is certain that very few of the earlier cases have been investigated in the light of what is now known of these particular subjects. It would thus appear probable that in this relatively short available period of time the rarity of calcosinosis has prevented any marked progress being made in our understanding of the condition. Furthermore, unless the frequency of its incidence should greatly increase, it is improbable that any considerable number of cases could be amassed for investigation as a group. The expedient of summarizing the work of many investigators, each usually concerned with single cases, becomes, therefore, a necessity. Comprehensive reviews of this kind have been made by Steinitz (65) in Germany, by Weissenbach, *et al.* (81) in France, and by Durham (18) in America. No such review has been found in British literature on the subject.

The clinical association of the disease with scleroderma or allied disorders, noted in the first reported case, and frequently observed since that time, has already been mentioned. The opportunity recently arose at St. Mary's

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Hospital, to study simultaneously and in some detail advanced but uncomplicated cases of both of these conditions. In the following paper an attempt will be made to summarize from the available literature the existing knowledge of calcinosis, and to add the results obtained in this investigation.

### *Clinical Manifestations*

Calcinosis is a particular example of pathological calcification in which multiple calcareous deposits occur in the skin, in the subcutaneous tissues, and also, in some cases, in the more deeply seated interstitial connective tissues. It is essentially a chronic disease, relatively unnoticeable in its onset, and tending thereafter to be slowly, though not uniformly, progressive.

A fair proportion of patients, especially if the disease begins in adult life, give a long history of diseases such as scleroderma, or of peripheral vasomotor neuroses of varying severity up to the full picture of Raynaud's syndrome. No other phenomena of known importance antedate the onset of the disease.

The earliest symptom is frequently a soreness or tenderness of localized areas of skin; while examination at such a stage as a rule reveals multiple discrete subcutaneous nodules, stony hard to palpation, differing greatly in size and quite irregular in shape, but tending on the whole to be flat and to form plaques rather than solid masses as extension and aggregation takes place. The smaller and earlier subcutaneous nodules are usually movable, larger plaques and those concretions in the deeper fasciae tend to be fixed to the surrounding tissue. The skin over the more superficial of these deposits sooner or later becomes red and inflamed, and ultimately breaks down with the formation of painful, indolent, and usually shallow ulcers. A low-grade secondary infection persists in such ulcers, and from time to time a chalky, purulent discharge may take place from the subjacent calcareous deposits. Some of these ulcers eventually heal, leaving behind a dense scar to mark the place where a concretion once was formed. In any given case it is usual to find all stages of these lesions present, from the earliest demonstrable nodule to the terminal healed scar.

The distribution of the lesions is a characteristic of the disease, for the deposits seem especially to be congregated in those positions where trauma is most likely to occur. Thus, the limbs are frequently involved, while the trunk, face, and scalp are almost always spared; and of the limbs it is in the fingers, about joints such as the elbows and knees, and at points of pressure such as the shoulders and buttocks where the majority of deposits are to be found. Neither at autopsy, nor on radiological examination, which demonstrates the deposits accurately and easily, has any internal organ or viscus been shown to be involved in any of the reported cases.

Lesions around joints may cause some limitation and difficulty in movement, even when the deposits are entirely superficial, especially if ulceration has occurred. Far greater restriction of movement, however, arises from the presence of more deeply seated concretions, which occur in the severest cases. Disability of this kind may indeed be the symptom of which the patient first complains. These latter deposits are found in fascia, and fibrous connective tissue, around muscles, tendons, and even nerves. They rarely cause pain except on forced movement of the joint or area affected, nor do they tend to come to the surface and ulcerate, but when extensive are frequently followed by muscular atrophy and contractures which tend to result in a crippling deformity.

Steinitz (loc. cit.) in reviewing the subject separated the reported cases into two clinical groups, which he entitled 'Calcinosis Circumscripta' and 'Calcinosis Universalis'; descriptive names given earlier to cases reported respectively by Reines (58) and Versé (75). He was able to amass seventy-one cases of the former localized form, and thirty-four cases of the generalized disease. In such a classification the following points of contrast appear:

(a) *Calcinosis circumscripta*. Occurring most often in adult women; in this form the deposits are limited to the skin and subcutaneous tissues, while in distribution it is the upper extremities, and especially the fingers, which are almost always affected, the remainder of the body as a rule not being involved. From the superficial similarity which exists between the appearance of these deposits and 'tophi', this type has also been called 'Calcium Gout', although it shows hardly any other close resemblance to the much commoner uric acid gout, and in particular has never been proved to be dependent on any analogous causal metabolic disturbance. Superficial ulceration with scar formation and some limitation of movement, as a rule occur, but although the condition is chronic it interferes little with the general health of the patient.

(b) *Calcinosis universalis*. Here multiple deposits occur, not only in the skin and subcutaneous tissues, but also in the deeper interstitial connective tissues. Furthermore, although the limbs bear the brunt of the lesion (the head and trunk being usually but not always spared) the deposits have a far wider distribution and tend to be much more extensive and numerous than in calcinosis circumscripta. It is characteristic, also, that the generalized form occurs most frequently in children, and has by far the worse prognosis. Limitation of movement, deformity, and widespread ulceration eventually enforce a bed-ridden life, and it would seem to be the rule that, following a progressive deterioration in general health, the enfeebled patient dies of some intercurrent infection.

Such a classification, widely accepted on the Continent and in America, is extremely convenient, but it is, perhaps, important to emphasize that no fundamental pathological distinctions have been shown to be present; moreover, cases of every grade of severity exist, and there is no clear dividing

line to be drawn between the two groups. It would, perhaps, be more accurate simply to state that when calcinosis affects children the deposits tend to be more extensive and widely spread, the disease more severe, and the outlook much more gloomy than is the case in adults.

### *Aetiology*

The problem of the aetiology of calcinosis has been discussed by almost every writer on the subject, and a number of hypotheses have been advanced.

Duret (16) reported cases in a brother and sister, but in no other instance in the literature has any evidence of a possible inherited tendency been found.

By far the greater number of cases have occurred in the white races of Europe and North America—a limitation which is probably entirely artificial, and due to the more numerous medical publications and facilities in these areas.

In Steinitz's series of cases calcinosis *circumscripta* occurred more frequently in females than in males, the ratio being approximately 6:1, while in calcinosis *universalis* the sex ratio was unity. In the same series the former variety of the disease appeared usually in middle life, and only very rarely in children; in the latter type the incidence of the disease with respect to age was reversed. Tisdall and Erb (72), Goldreich (25), and Swanson, Forster, and Iob (68) have recorded the occurrence of calcinosis in infants under 2 years of age.

The association of calcinosis with other diseases is of extreme interest and aetiological importance. In the interval between Weber's case and 1911, Thibierge and Weissenbach (70) were able to collect nine cases of the combination of calcinosis and either scleroderma or sclerodactylia; and in the French literature of to-day this syndrome bears their names. In the literature to which we have had access, of a total of 121 cases, thirty-eight were examples of this association. Similarly, Steinitz found that more than one-third of the cases of calcinosis *circumscripta*, and nearly one-quarter of those of calcinosis *universalis* occurred in conjunction with this disease. It is also of aetiological significance that in the combination of these two diseases the distribution of the skin lesions and the calcification is almost invariably similar.

Raynaud's syndrome, less severe vasomotor neuroses, such as chilblains or acrocyanosis, are also very frequently co-existent with calcinosis. Such a combination has been recorded by Hutchinson (32), Langmead (42), Meachen (50), Hunter, W. K. (31), Logan (48), Lewy (47), and Brauer (11), to mention only a few; while Durham (*loc. cit.*), in presenting such a case, has reviewed and discussed the relationship between calcinosis, scleroderma, and Raynaud's disease.

Muscle fibrosis has also been found to be associated by Bertolotti (10), Oehme (53), Weissenbach *et al.* (82), Hunter, W. K. (*loc. cit.*), and Langmead (43). The latter discussed cases of scleroderma, calcinosis, dermatomyositis, and myositis fibrosa, and gave reasons for his belief that these conditions were clinical manifestations of one disease. However, as Barr (5) pointed out, many cases of severe calcinosis fail to show any recognizable evidence or history of scleroderma, or of fibrosis of muscle, while still more examples of these latter diseases are uncomplicated by calcinosis. There remains the possibility, nevertheless, that individual differences may be responsible for the various clinical pictures arising from the underlying hypothetical single cause. Bearing in mind the significant fact that these are rare diseases, and yet, when they occur they often co-exist in the same patient; the position may, perhaps, best be summed up by saying that, while *a priori* grounds for a causal relationship exist, much more evidence of a fundamental kind is needed either to prove or disprove Langmead's contention.

Accurate studies of the metabolism in this disease have been possible only in the last few years. Previously, in investigations of this kind, Vaninini (74) and Umber (73) had reported inconclusive results in two cases of calcinosis circumscripta. Later, Staub (64) and Swanson, Forster, and Iob<sup>2</sup> (*loc. cit.*), also in cases of the localized form of the disease, were unable to demonstrate any constant abnormality of calcium and phosphorus metabolism. In this connexion Thannhauser (69) has suggested that it is unnecessary to invoke an underlying metabolic disturbance as the basis of the localized form of the disease; since the frequency of the circulatory disturbance in the hands and feet of these cases, the known failing local nutrition, and the high incidence of gangrene in Raynaud's disease and scleroderma, with which they are so often associated, strongly raise the possibility that the calcification may be an expression of local tissue damage, analogous to that formed in infarcts, in old tuberculous lymph nodes, or indeed in any of the varieties of dystrophic calcification which may occur in the body.

Two more extensive investigations have been made of the metabolism in severe cases of generalized calcinosis. Friedländer (21), studying complete mineral balances in such a case, was unable to show any departure from the normal, and in particular found no abnormality in calcium metabolism. Bauer, Marble, and Bennett (8), however, in some carefully controlled and extensive studies of the calcium, phosphorus, and nitrogen balances, showed their case to have a very marked tendency to retain absorbed calcium and phosphorus, the retention being greater for calcium. Since, in their case, also, radiological examination did not reveal increased bone density, they concluded that local abnormality of the soft tissues gave rise to a disordered

<sup>2</sup> However, in this case the diet consisted of cow's milk and cod-liver oil, under which conditions an increased output of calcium would be expected.

calcium and phosphorus metabolism, which seemed of fundamental importance in the disease.

In both these latter cases the values for calcium and phosphorus in the blood remained within normal limits during the period in which they were investigated. Similar normal values have been found in the majority of the cases in the literature in which serological investigations have been made—some thirty cases—but, on the other hand, abnormal values have been recorded. Of these, Mosbacher (52), Akobdszanjanz (2), and Pulay (56) reported levels of calcium so high as to throw doubt upon the accuracy of their determinations. Significant high values have, however, been found by Staub (64), Wiedman and Shaffer (79), and Lewy (47) in *calcinosis circumscripta*, and by Schultze (59), Hein (27), and Skosogorenko (63) in *calcinosis universalis*.

Some authors, notably Tisdall and Erb (72), and Wilens and Derby (85), have argued that abnormality of metabolism in *calcinosis* could be excluded on the evidence of a maintained normal serological level of calcium and phosphorus. The vast amount of recent investigation of the conditions under which these elements exist, and of the factors governing their amount in the body fluids, critically reviewed of late by Peters and Van Slyke (55), and Thomson and Collip (71), shows beyond doubt that many factors other than the mutual interdependence of calcium and phosphorus under these conditions, profoundly modify both their amount and their physiological activity. Furthermore, this work, and particularly the investigations of Aub and his co-workers, and Hunter, D. (30), has abundantly proved that even with complete serological studies, the level of calcium and phosphorus in the blood is of no value as evidence of normal metabolism, or of retention, or of loss of these elements by the body when unaccompanied by metabolic studies.

The evidence for a metabolic disturbance in this disease is therefore conflicting, and more studies of this type are needed. If any conclusion may be drawn from such a diversity of recorded fact and opinion, it is the possibility, in a chronic disease of this type, of the occurrence of alternating phases of activity and inactivity in which abnormality of metabolism, if it occurred, might only be detectable in the former. Certainly clinical study of this disease would indicate that the calcareous deposits do not accumulate steadily; rather, on the contrary, long periods of apparent quiescence occur, only to be interrupted at length by the appearance of fresh lesions.

The coincidence in some cases of the onset of *calcinosis* with the time of the menopause led Weil and Weissmann-Netter (80), and Wolf and Valette (86), to suggest that the disease might be related to an endocrine disturbance. This remains a possibility, for, if *calcinosis*, as Thannhauser suggests, is a variety of dystrophic calcification secondary to circulatory insufficiency, then endocrine imbalance, which is becoming an increasingly recognized factor in such circulatory disturbances, might well provide a cause for its onset. On the other hand, it is certain that the endocrine system is a highly important factor in the regulation of calcium metabolism.

Moreover, metastatic calcification is now a clinically well-recognized feature of hyperparathyroidism as Hunter, D. (29), and Barr and Bulger (6), have been able to show in recent reviews, while similar metastatic deposits have been produced experimentally by Hueper (28), and many others, by administration of parathormone in large doses. It is also of interest in this connexion that Seyle (60) found that parathyroid extracts not only gave rise to metastatic calcification, but also, in young rats, caused a proliferation of subcutaneous fibrous tissue, giving, at last, an advanced experimental sclerodermia. In clinical and experimental hyperparathyroidism, however, there results characteristically (a) hypercalcaemia, (b) hypophosphataemia, and (c) an abnormally great excretion of calcium and phosphorus, findings which are utterly unlike any of those of the metabolic studies reported in calcinosis. Furthermore, it is invariably found in any type of metastatic calcification that calcification of the organs and viscera occurs—a distribution which never appears in calcinosis. Finally, in the only case so investigated, at post-mortem examination Durham (17) found the parathyroids to be microscopically and macroscopically normal.

Aub, Bauer, Heath, and Ropes (4) have shown that disorders of the thyroid gland are productive of change in calcium metabolism, unaccompanied by changes in the serum calcium, and, in particular, hypothyroidism was found to be associated with a decreased excretion of calcium and phosphorus. However, with the exception of Bertolotti's case (10), where hypothyroidism and hyperpituitarism were diagnosed on evidence which would now be regarded as incomplete, neither calcinosis nor metastatic calcification have been reported in association with such disorders.

On less secure grounds are the claims of Leites (46), that the thymus and the gonads play a part in calcium metabolism respectively synergic and antagonistic to that of the parathyroids.

On the whole, the changes which result from known endocrine disorders are unlike the changes which have been found to be present in calcinosis. It is apparent that very much more evidence, particularly of the state of the endocrine system, in cases of calcinosis, is needed before the aetiological importance of this system in this disease can become more than an interesting speculation.

Finally, in view of the facts, (1) that metastatic calcification may easily be produced experimentally by toxic doses of Vitamin D, and (2) that Rabl (57), Dreyfuss (15), Stephens and Barr (67), and others, have shown that similar calcification results in animals on acid diets rich in calcium and phosphorus, it is perhaps of importance to state that, while details as to the natural diet of patients with calcinosis are rarely mentioned in the literature, there is no evidence that their customary diets were in any way abnormal. Here, too, the fundamental difference in the distribution of the lesions in known metastatic calcification and in calcinosis makes it difficult to correlate them.

*Pathology*

In relatively few cases have complete pathological examinations been reported.

The association with scleroderma and Raynaud's disease has been noticed in these examinations, just as it has in the clinical investigations of these cases. It is perhaps important, too, that a small but significant number exhibited also chronic nephritis. In general, however, no constant abnormality apart from the deposits and the changes resulting immediately from their presence has been proved to exist.

It is also unfortunate that histological study and chemical analysis of the deposits themselves are seldom disclosed, for the results from such an investigation might be expected to do much to establish definitely the position of calcinosis as a variety of pathological calcification, when it is remembered that dystrophic calcification is, as a rule, preceded by demonstrable local necrotic changes, while metastatic calcification occurs with no evidence of previous local tissue damage.

Versé (75) stated that the earliest evidence of the lesion was to be found in a colloid swelling of the connective tissue, and that this was followed by a deposition of calcareous granules in the fibrils of connective and elastic tissue within such living fibrous masses. Parkes-Weber (54) reported similar findings. In Wilens and Darby's case (85) the earliest deposit appeared in the subcutaneous fat, within and between fat cells. Bauer, Marble, and Bennett also reported the early lesions as occurring in and around intact fat cells, with subsequent inflammatory reaction, foreign body giant cells, and fibrosis. None of these authors found any evidence of preliminary necrosis. On the other hand, Hunter, W. K. (31), Morse (51), and Lecene and Moulouguet (45) reported cases in which calcification occurred in subcutaneous tissue following fat necrosis. Thibierge and Weissenbach found that calcification took place in preformed masses of fibrous tissue which had first always undergone hyaline degeneration, while similarly, Tisdall and Erb (72) gave evidence of preliminary degenerative changes in fibrous tissue as antedating the calcification in their case. Histological evidence is therefore conflicting.

Chemical analysis of the concretions has shown them to consist of tertiary calcium phosphate,  $\text{Ca}_3(\text{PO}_4)_2$ , Wolf and Valette (86), or a mixture of tertiary calcium phosphate and calcium carbonate, Wilen and Darby (85), Steinitz (75), Bauer, Marble, and Bennett (8), Gascard (23), and Harlay (26). In the reports of the last three authors, quantitative analyses of the deposits were made, and after due allowance for calcium combined as carbonate, the ratio of calcium to phosphorus was in each case shown closely to approximate to that found in normal bone by Kramer and Shear (41), and in other forms of pathological calcification by Wells (83), and Wurm (87). Hunter, W. K. (31), found evidence of traces of magnesium.

Where adequate analysis has been made, organic constituents of the deposit seem either to be entirely absent or present in minimal amounts.

The classification of calcinosis, either as a unique and separate variety of pathological calcification, or as a form of either dystrophic or metastatic calcification, thus remains unsettled.

### *Diagnosis*

The diagnosis of calcinosis may be made by recognition of the deposits, which are characteristic in type and in distribution. A history or the co-existence of Raynaud's disease, less severe vasomotor neuroses, myositis fibrosa, or scleroderma in a patient in whom calcinosis is suspected, will strengthen such a suspicion. Of assistance in diagnosis, also, is the probability that the presenting symptom or symptoms will arise from one of two causes: (a) irritation and eventual ulceration of the skin overlying superficial deposits; (b) disability occasioned by deep-seated deposits.

Removal of one of the nodules and its subjacent deposit for histological and chemical study will help to confirm the diagnosis. In view of the conflict of opinion as to the exact pathology and aetiology of the condition, other laboratory or metabolic studies, though of great interest in a study of the disease, are as yet of little help in diagnosis.

The decisive examination is likely to be radiological, whereby the multiplicity and the exact localization of the lesions will be far better demonstrated than by any other means. Especially is this so in those early or mild cases where few of the deposits are visible or palpable. Indeed, a proportion of such cases will be found during radiological examinations made for quite extraneous reasons. Such an examination will also go far to distinguish calcinosis from other diseases with which it may be confused.

In the differential diagnosis it is important to distinguish the following: (1) Forms of dystrophic calcification; for example, calcified lipomata, phleboliths, and calcified tuberculous lymph nodes. (2) Forms of metastatic calcification, such as have been reported occasionally to be associated with nephritis by Virchow (76), with multiple myelomata by Wallgren (77), in leukaemia by Wells (84), and also in sarcoma and in carcinoma (44), (33), in osteomyelitis (38), and in hyperparathyroidism (9), (29). (3) Uric acid gout. (4) Myositis ossificans and myositis ossificans progressiva.

Most difficulty may be encountered in cases of dystrophic calcification. Here, however, the previous history and symptomatology, the localization of the lesions, and their distribution, will rarely simulate that of calcinosis, while examination of a biopsy specimen should frequently settle the question.

### *Prognosis*

In most cases, especially when the onset occurs in adult life, calcinosis, although it will probably persist for life, rarely seriously impairs the general

health. Certainly it is not infrequently compatible with longevity (66), (81). The disease in these milder forms—calcinosis circumscripta—seems to attain in each case a certain level of severity and there remain; for, while fresh deposits occasionally form, enlarge, and very slowly ulcerate, as slowly and as occasionally old ulcers heal, following the eventual discharge of the underlying deposits. There is evidence, also, that occasionally superficial nodules may be reabsorbed before ulceration occurs, but it must be rare indeed in an adult for a cure to take place. Swanson, Forster, and Iob (*loc. cit.*) report a case, classified as calcinosis circumscripta, in an infant, in which the onset was at the age of 5 weeks, and in which the lesions had completely and spontaneously disappeared at the age of 8 months. Cures have also been reported, in the more severe generalized form, by Kennedy (37), and by Craig and Lyall (14), while the patients (children) were under treatment for the condition. As a rule, however, the prognosis in severe generalized cases is bad. Such examples of the disease represent nearly a third of all the reported cases, and the patients are frequently children. It appears not improbable that the major factor underlying the serious outlook for these patients is the gross disability and deformity consequent upon their extensive lesions, which sooner or later lead to a bed-ridden life. Here the extensive ulceration, and the lack of mobility will play a large part in the production of a chronic ill-health, muscular wasting, and asthenia, and render the patient liable to chance but fatal infection.

#### *Treatment*

In very few cases of calcinosis has therapy been followed by cure; in a few more, significant results were obtained which were suggestive of improvement, and promised eventual recovery; while, finally, spontaneous cure is not unknown.

The observation of Frolich (22) that a generalized acidosis favoured the elimination of calcium, led Kennedy (*loc. cit.*) to prescribe a ketogenic diet in his case. He was able to report a cure after some three years' treatment. Acidosis induced by ammonium chloride administration was used by Bauer, Marble, and Bennett (8), and Skosogorenko (63). The former were able to show that a previously persistently positive calcium balance was replaced by a negative balance which they were able to maintain. The latter reported a fall in serum calcium from 13.6 to 8 mg. per 100 c.c. In both cases there were some indications of clinical improvement. Other methods of increasing the output of calcium are available, for both active parathormone and vitamin D preparations are obtainable. Their use is not advised; for, apart from the danger of an induced metastatic calcification, notwithstanding increased calcium output, their value in decalcifying abnormal deposits is apparently negligible, as Albright, Bauer, Ropes, and Aub (3) have shown in the case of parathyroid extracts. In this connexion, while Aisenberg (1) has used heliotherapy in calcinosis without success, Hein (27) on the other

hand demonstrated improvement in a severe case of the generalized form by a therapeutic combination of natural and artificial sunlight.

The treatment of calcinosis by increasing calcium elimination has the theoretical disadvantage that decalcification of the skeleton would seem almost certain to occur; indeed the relatively great bulk of the skeletal tissues as compared with that of the deposits would make it appear probable that the major part of the excess calcium eliminated will be of that origin. In many cases it may therefore not be possible considerably to affect the deposits without dangerously decalcifying the bones.

Since it has been amply shown that the absorption of calcium and phosphorus is greatly reduced by increasing the alkalinity of the gastro-intestinal tract (34), (55), it would appear theoretically possible that by so diminishing the intake, the skeleton, in competing for an inadequate supply of calcium, might induce decalcification of the deposits. Craig and Lyall (14) used this method when they treated and reported a cure of their case with alkaline sodium phosphate ( $\text{Na}_2\text{HPO}_4$ ).<sup>3</sup>

Symptomatic treatment is still, perhaps, the most important aspect of medical care in these cases. Adequate treatment of the ulcers is difficult. In the milder forms of great chronicity, curetting, or even excision of troublesome deposits, may in some cases be worthy of trial, even though others will almost certainly eventually appear.

In view of the chronicity of the condition, pain caused by the lesions, which is rarely severe, is best treated by an analgesic such as aspirin. Local dressings, antiseptics, and astringent preparations will contribute greatly to the comfort of the patient.

The treatment of the disability and deformity arising in severe cases presents an orthopaedic problem, which varies with each case. Erb (19) has discussed the methods available. In severe cases the very highest nursing skill is needed to prevent the development of bed-sores, and to maintain a satisfactory level in the general health of the patient.

#### *Case Reports.*

*Case 1.* E. G. A girl aged 15 was readmitted for investigation to the wards of the Medical Unit of St. Mary's Hospital in November 1931.

*Past History.* The patient had whooping-cough, measles, and chicken-pox before the age of 5. For as long as she could remember she had suffered from cold hands, and invariably developed extensive chilblains in winter. She was admitted to a hospital for Nervous Diseases at the age of 10, in 1926, for disability, pain, and swelling of the arms and legs, was diagnosed as an early myopathy, and was discharged after symptomatic treatment. On readmission two years later the disability had increased so that she was unable to walk upstairs, or accurately use her hands. Pain, and swelling of the forearms, fingers, thighs, and calves without oedema were again present. She was admitted to St. Mary's Hospital in 1929, on the development of

<sup>3</sup> Should this cause a rise in the level of phosphorus in the blood it will induce an increased excretion of calcium, as Greenwald and Gross (24) and others have shown.

indolent ulcers in front of both patellae. Radiological examination revealed other deposits, and a diagnosis of calcinosis was made. Menstruation began, in hospital, at the age of 13, and since then it has continued scantily and irregularly, with long intervals between the periods. Symptomatic treatment gave relief, and she was discharged, to be followed up in the Out-Patient department.

*Family History.* No similar case was known in the family in the last three generations, nor was there a history of any allied disease such as sclerodermia.

*Physical Examination.* The patient seemed a well-developed girl of 15, flabby and phlegmatic in type, and manifesting rather an excess of subcutaneous fat. Examination revealed severe generalized calcinosis. Shallow ulcerations were evident about the knees, elbows, and wrists, while other superficial deposits in all stages of development could be seen or palpated on the fingers, forearms, arms, buttocks, and thighs. They were especially prevalent near joints. With the exception of two small submental concretions, the head, trunk, and abdomen seemed unaffected. Deep-seated, extensive masses could be palpated in the thighs and popliteal spaces, around the buttocks, and near the elbows. Some limitation of movements of fingers, and of the wrist and elbow-joints was present, very much more limitation of movement was noticeable in both hip and knee-joints. As a result, her gait was peculiar and stiff, and she had difficulty with obstacles such as stairs. The functional ability of the upper extremities was less impaired, although fine movements with certain fingers were poorly executed. There was, in addition, an evident weakness in all the limbs, and though they appeared normal in shape to palpation the muscles were markedly abnormal. Thus, for example, the calves and muscles of the arm and forearm were felt to be considerably smaller than appearance would have suggested, and they lacked that firm resiliency of normal muscle, seeming tougher and altogether less elastic. The hardness of the muscles was the more remarkable in view of the fact that the patient had been confined to bed for eighteen months. There was no oedema demonstrable.

The skin, in areas unaffected by concretions, while it was always rather rough and dry, showed no marked abnormality, except on the hands, which tended to be cold and somewhat cyanotic, and which during the winter from time to time exhibited chilblains. Sight was quite normal, as were the ocular fundi, while examination of the lenses by slit-lamp microscopy revealed no opacities or calcareous deposits.

The cardiovascular, respiratory, central nervous, genito-urinary, and gastro-intestinal systems were quite normal. There was no demonstrable abnormality of the endocrine system, save the irregularity in menstruation.

*Course in Hospital.* During the patient's stay in the hospital she twice had mild urinary infections, accompanied by slight pyrexia, which cleared up on treatment with alkali. With these there was no demonstrable change in the condition of the calcareous lesions.

She was allowed to be up and about the ward during the most of the period except during the above episodes. Until therapy in the form of disodium hydrogen phosphate was begun, the patient's clinical condition seemed to be slowly and irregularly progressive. An exacerbation in the soft tissue calcification happened to coincide with the first investigation of her Ca and P metabolism.

She was discharged, relieved, on July 5, 1932.

*Laboratory Findings.* (1) Urine. During the periods of infection traces of albumin, and a few leucocytes, and bacteria were found. Apart from these periods, the urine was normal throughout to routine qualitative tests. (2) Blood. Blood count, cell morphology and haemoglobin normal. Wassermann reaction negative. (3) Blood urea. 23 mg. per 100 c.c. (4) Renal function tests (Calvert's modification of MacLean's and Volhard's tests, together with examination of the urinary sediment) were within normal limits. (5) Basal metabolic rate. (Average of three closely approximating determinations) = +5.1 per cent. (6) Serum calcium. 12.2 mg. per 100 c.c. (7) Plasma inorganic phosphate. 7.67 mg. per 100 c.c. (8) Plasma phosphatase. 0.331 units.

Laboratory data, therefore, with the exception of the latter three, were normal. The serum calcium, plasma inorganic phosphate, and plasma phosphatase were followed over a period of some months, and their fluctuations will be shown in tabular form.

*Radiological examination.* A complete examination of the whole body was made. No evidence of any calcareous deposits was found in any viscus, and in particular, no biliary or renal calculi were demonstrable. The pituitary fossa was normal, while the neck and superior mediastinum were examined specially, but failed to show any evidence of parathyroid adenomata, of substernal enlargement of the thyroid, or of thymic hyperplasia. The limbs, the trunk, and head showed no deposits other than a single one in the chin at the symphysis menti; another such single deposit was found behind the right os calcis. The appearances in the radiogram are easily recognizable as pathological calcareous deposits in the soft tissues. They vary much in size, form, and character, ranging from formless smears to separate, well-defined deposits with sharp outlines, grouped in masses or in long streaks within or about muscles, sometimes outlining them, or as isolated flat masses in the subcutaneous tissues and pulp of the fingers. Close inspection of the radiogram may show loss of tissue over a mass and the deposit presenting at the surface. There was wasting of the lower end of the right thigh, well seen in the original film, though not obvious in the print, and with it a deformity of the growing end of the right femur. The latter also showed some secondary disuse atrophy, as did the bones of the right foot. It is possible that muscular atrophy and fibrosis may have played a part in the production of the deformity. All the bones showed diminished calcium content, particularly the cancellous bone, as proved by increased transradiancy and open structure as compared with a normal control of the same age, sex, and size, who was exposed under exactly similar conditions, using one plate only for patient and control. The medullary spaces tended to be widened, and the cortex as a rule appeared thinned. It is of considerable interest that the epiphyses were advanced by about three to five years. No bone was demonstrable in the deposits, and no intra-articular deposits could be seen, the joint surfaces being smooth and joint spaces well preserved. Comparison with radiograms made in 1929 indicated that the disease had progressed and extended considerably during the intervening three years. A further examination after a period of eight weeks' therapy with alkaline sodium phosphate showed a very marked reduction in the extent and density of the deposits, a change unaccompanied by demonstrable alteration in the radiographic appearance of the bones. Radiological examination in November 1933 after more than a year's therapy showed still further reduction of the deposits, and this was

particularly evident in the deep-seated lesions, as Pl. 19 (Fig. 2) shows. The calcium content of the bones seemed unaltered.

*Biopsy specimens.* Under local anaesthesia, two subcutaneous nodules were removed from the forearms by Dr. R. B. D. Wright; the wounds healed by first intention.

#### 1. Chemical analysis.

(a) Qualitative: (1) Calcium present; (2) Magnesium absent; (3) Carbonate and phosphate present; (4) Uric acid (if present) in minimal amounts—murexide test negative; (5) Oxalate absent.

(b) Quantitative: Calcium = 18.08  
Phosphorus = 8.41 } gm. per 100 gm. dry wt. of  
CO<sub>2</sub> = 2.49 } specimen.

If the calcium assumed to be present in the form of calcium carbonate is subtracted from the total calcium content, it is possible to obtain a calcium to phosphorus ratio comparable with those found in normal bone and in other pathological calcifications. Thus:

$$\frac{\text{Residual Ca}}{\text{Residual P}} = \frac{\text{Total Ca} - \text{Ca (carbonate)}}{\text{Total inorganic P}}.$$

Calcium present in concretion as CaCO<sub>3</sub> =  $2.49 \times \frac{40}{44} = 2.27$  gm.

$$\frac{\text{Residual Ca}}{\text{Residual P}} = \frac{18.08 - 2.27}{8.41} = 1.88$$

This value agrees well with the theoretical  $\frac{\text{Ca}}{\text{P}}$  ratio of 1.94 for Ca<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub>, and with the values found in normal bone, and in pathological calcifications of this and other types.

*Histological study.* Two specimens were taken. One had ulcerated, and a large part of the deposit had been discharged. The calcareous material remaining was in a thick mass of fibrous tissue continuous with the cutis, some of the elastic fibres running deep into the lesion. The sinus whence the material had escaped was coated with squamous epithelium, and led to a cavity lined with granulation tissue in which were many foreign body giant cells. Some of the deposit was still present in this cavity. Around it there was much fibrosis with considerable hyaline degeneration, and a patchy deposition of material containing calcium in the degenerate collagen. The other, an earlier nodule which had never ulcerated, showed large masses of calcareous material in the cutis and fibrosed subcutaneous tissue. A few islands of fat could be seen cut off by calcified collagen fibres. Most of the calcareous material was lying surrounded by fibrous connective tissue only, but at the edges where the deposition had occurred most recently there was a well-marked inflammatory reaction with foreign body giant cells. In none of the sections was any split or phagocytosed fat seen, nor did the deposit anywhere appear in fat cells. It would seem probable that the calcareous deposit first occurs in the abnormal fibrous tissue of the cutis or deeper structures. It causes a foreign body inflammatory reaction with the formation of multinucleated cells and granulation tissue. As the latter organizes more fibrous tissue is formed. This undergoes, in turn, a hyaline change, becomes calcified, and initiates a new inflammatory reaction, and so the cycle of changes continues.

*Case 2. (Sclerodermia.)* L. F., a female, aged 41, was admitted to St. Mary's Hospital under Dr. T. C. Hunt in February 1932.

*Past history.* The patient could remember no serious illness in the course of her life. She had, however, always been subject to skin complaints of various kinds, such as acne vulgaris, impetigo, eczema, and the prolonged suppuration of small wounds. Early in 1930 she developed a febrile illness, diagnosed as influenza, and since that time had been unwell. In that illness and during the intervening year she experienced in the legs, arms, and face, pruritus and a constant burning pain,—and in these areas the skin became irregularly flushed, hot, and red. Pyrexia is known to have occurred at irregular intervals during the year.

The character of the skin rapidly and progressively changed, becoming thick, inelastic, hard, and shining, the process seeming to begin patchily in the flushed areas; the latter then extended, coalesced, and so advanced until a considerable proportion of the skin of the body was involved. Beginning, and always worst in the limbs and face, the lesion spread and increased in severity until nearly the entire body's surface was abnormal.

Joint movement became increasingly difficult and painful, so that by December, 1932, she was bed-ridden, being unable appreciably to bend her fingers, wrists, elbows, ankles or knees. From the onset of the condition she lost weight, and on admission weighed 43 lb. less than had been the case a year previously. Her menstrual history was normal.

*Family history.* No similar case was known to have occurred among the relatives or ancestors. Her family were all unusually subject to minor skin affections, and particularly liable to a difficulty in the healing of small skin wounds.

*Present condition.* The patient was emaciated and looked severely ill. Over the face, all four limbs, and a large part of the trunk the skin was thick, shiny, and semi-transparent. Her colour was generally normal, or nearly so, except on the trunk where red, flushed areas indicated active spread of the disease. Here also the skin was hypersensitive to touch. Nearly complete obliteration of the normal skin creases had occurred.

The face was mask-like. Respiration was unduly abdominal in type, while there was an extreme limitation of movement of almost all the limb joints; moreover any forced movement of these joints was very painful to the patient. It was apparent that the skin condition was the factor responsible for the above. There were no calcareous deposits, and physical examination was otherwise negative.

During her stay in the hospital the patient maintained an irregular pyrexia for which no cause other than active sclerodermia could be ascertained. It was only with extreme difficulty that bed-sores were controlled, and her course in the hospital was steadily downhill.

A fortnight after leaving the hospital at her own request, the patient died; a post-mortem examination was not obtained.

*Laboratory investigations.* (1) Urine. Traces of albumin were occasionally present; otherwise normal to routine tests. (2) Blood. (a) Wassermann reaction negative. (b) Blood count, repeated at frequent intervals, showed a polymorphonuclear leucocytosis varying from 15,000–20,000, and a marked secondary anaemia. Haemoglobin = 52 per cent. (c) Blood culture repeatedly negative. (d) Serum calcium—10.9 mg. per 100 c.c. (e) Plasma inorganic phosphate—3.32 mg. per 100 c.c. (f) Plasma phosphatase—0.180 units. (3) Bacteriological investigation. (a) Teeth (which showed

definite pyorrhea alveolaris) and faeces gave evidence of a predominant *Streptococcus viridans* infection. (b) Throat and maxillary antra gave normal flora. (4) Radiological examination. (a) Bones and joints. Some disuse atrophy was evident in the former, while the latter, apart from minor arthritic changes in the knees, were normal for a woman of her age. No abnormal calcareous deposits were found. (b) Cholecystogram was normal. (c) Chest—lungs and heart normal.

*Biopsy specimen.* A histological study of an area of skin was made while in King's College Hospital. We are indebted to that hospital for the report that it was typical of sclerodermia.

*Therapy.* During her stay in the hospital the major therapeutic measures consisted of: (1) Blood transfusion. (2) Dental extraction (complete) for pyorrhea alveolaris. (3) Autogenous vaccine therapy, and 'Lacarnol' injections subcutaneously. (4) Symptomatic treatment for the relief of pain, together with special nursing precautions.

*Methods.* In this study the various quantitative chemical analyses of the biopsy material, of the blood, and of the excreta in the metabolism experiments were made, with one exception, in duplicate throughout. In each the average value was taken as representative. On three isolated occasions a divergence between the duplicate readings was sufficiently great to necessitate a third determination, which was accordingly made, and the average between the two most closely approximating results was taken.

In the patient with sclerodermia the skin condition was such that adequate amounts of blood could be obtained only with the greatest difficulty. In her case, therefore, duplicate determinations of the levels of calcium, phosphorus, and phosphatase in the blood were not made.

The methods of analysis employed were as follows:

(a) *Blood chemistry.* The serum calcium was estimated by the Kramer-Tisdall method as modified by Clark and Collip (13), the plasma inorganic phosphate by the Briggs's modification of the Bell-Doisy procedure (12), and the plasma phosphatase by the method of Kay (36).

(b) *Chemical studies of the biopsy specimens.* (1) Calcium and phosphorus. 0.1 gm. of the dried material was weighed into a platinum crucible, and ashed over a free flame. The ash was dissolved in a few cubic centimeters of 50 per cent. hydrochloric acid, and the solution made up to 100 c.c. with distilled water. In this solution the calcium was determined by Clark and Collip's method, and the phosphorus by Briggs's method as above. (2) Carbon dioxide. A known weight of the dried material was taken, and the carbon dioxide obtainable determined by the method of Shear and Kramer (61).

(c) *Metabolism.* The case of calcinosis, a normal control of the same age, sex, weight, and build, and the case of sclerodermia were given a carefully weighed diet containing low (but known) amounts of calcium and phosphorus (approximately 100 and 700 mg. per diem respectively), but adequate in all other respects. All three were kept on this diet for a period of at least a fortnight before the observation periods were begun. Salt and fluid intake were also maintained at a constant known level. In the cleaning of the necessary utensils, and in the preparation of food and drinks only distilled water was used.

Urine was collected in twenty-four hour specimens in chemically clean bottles containing a trace of toluol, while its reaction was controlled to be

approximately neutral or just alkaline to phenolsulphonephthalein by the oral administration of sodium bicarbonate.

The faeces were divided into three-day periods by giving 0.3 gm. of carmine alum lake by mouth every third day, and the stools were passed regularly and unformed following the free use of liquid paraffin as a laxative—more drastic measures to prevent constipation being unnecessary.

When on occasion a patient (sclerodermia) was unable to take her full diet, the rejected food was collected, and separately analysed for its calcium and phosphorus content.

Calcium of the urine was determined by the method of Shohl and Pedley (62), in the food and faeces by the method of McCrudden (49); phosphorus was determined by the method of Fiske and Subbarow (20).

In each case, for the purposes of comparison, the intake and output of calcium and phosphorus were observed for three consecutive three-day periods; the effect of therapy in the case of calcinosis was subsequently further investigated, and in this patient the low calcium, low phosphorus diet was maintained permanently.

### *Discussion*

In the metabolism data, presented in Tables I and II, and illustrated in Fig. 3, the values for calcium and phosphorus are expressed in grams per three-day period. It will be seen that the normal control and the case of sclerodermia tended to give negative calcium and phosphorus balances on the diet given. On diets of this type this is essentially the normal response, as Bauer, Albright, and Aub (7), and many others have shown. Furthermore, in these cases the ratios of urinary to faecal calcium and phosphorus excretion are within normal limits. Finally, during the periods of observation the levels of calcium, phosphorus, and phosphatase in the blood of the patients were normal. It would appear, therefore, that in the case of sclerodermia, which was uncomplicated by calcinosis, the calcium and phosphorus metabolism was normal.

The case of calcinosis gave markedly abnormal results. On an inadequate intake this patient was nevertheless able to maintain positive calcium and phosphorus balances. She excreted approximately 0.17 gm. of calcium and 0.71 gm. of phosphorus less than the normal control per three-day period. Under the conditions of the investigation the faecal excretion of calcium and phosphorus was approximately normal. The urinary output was extremely low. There was, therefore, some evidence of a normal absorption of these elements, and presumptive evidence for an increased retention. At this time, as previously, the levels of calcium, phosphorus, and phosphatase in the blood were all abnormally high (Table IV). In this connexion it is, perhaps, significant that the work of Kay (35) would suggest that elevation in the plasma phosphatase is some indication that active calcification is proceeding. There were no symptoms or signs of kidney disease, and the renal function tests were essentially normal. It would, therefore, seem unlikely that renal damage sufficient in degree to cause such abnormalities, if that were possible, was present. Finally,

radiological examination, taken under standard conditions during the patient's stay in the hospital, failed to indicate any increase in bone density.

It seems, therefore, logical to conclude that there was an abnormality of calcium and phosphorus metabolism in this patient, and that her soft tissues showed an abnormal ability to retain these elements.

Therapy in the form of disodium hydrogen phosphate produced definite changes (see Fig. 3). Those referable to the clinical and radiological findings are described elsewhere. Metabolic data indicate that with the doses of this salt given approximate equilibrium in calcium metabolism was attained. The urinary output was very slightly increased but was still abnormally low, while the bulk of the increased excretion occurred in the faeces. Her faecal calcium output per three-day period was 0.08 gm. greater than that of the normal and 0.09 gm. greater than her own previous output on the diet alone. There is evidence, therefore, that the procedure caused a diminished absorption of calcium. The phosphorus balance remained positive, in spite of an increased excretion, a greater increase in the output occurring in the urine than in the faeces. Thus, while retention of phosphorus had increased, the excretion of calcium had been augmented until equilibrium in its metabolism had been attained. It was apparent, therefore, that factors other than the simple retention and deposition of a compound of calcium and phosphorus were present in this case.

As will be seen in Table IV, following this therapy, the level of calcium in the blood fell, and had reached normal limits in twelve weeks; plasma phosphatase also returned to normal, while the plasma inorganic phosphate at first increased and later fell again to approximately its old high value.

### *Therapy*

In view of the considerable degree of decalcification and some actual deformity which radiological examination had shown already to be present in the skeleton of this patient, it was considered inadvisable to increase the elimination of absorbed calcium and phosphorus by the production of an acidosis, lest in attempting in this way to decalcify the deposits, a further and dangerous depletion of the supporting structure of the bones might occur.

A safer and more promising method of reducing the deposits appeared to be afforded by limiting the absorption of these substances. This was accordingly done: (1) by limiting the intake by a diet very low in calcium and phosphorus, and (2) by giving alkaline sodium phosphate in amounts sufficient to change the reaction of the gastro-intestinal tract in the direction of alkalinity. Metabolic studies showed that 3 drachms of this phosphate per diem induced approximate equilibrium in the calcium intake and output on the above diet. It was hoped that by maintaining these conditions for

a long period the need of the relatively bulky skeletal tissues for calcium might lead to the decalcification of the deposits. After approximately eight weeks of this therapy, while little change could be demonstrated clinically

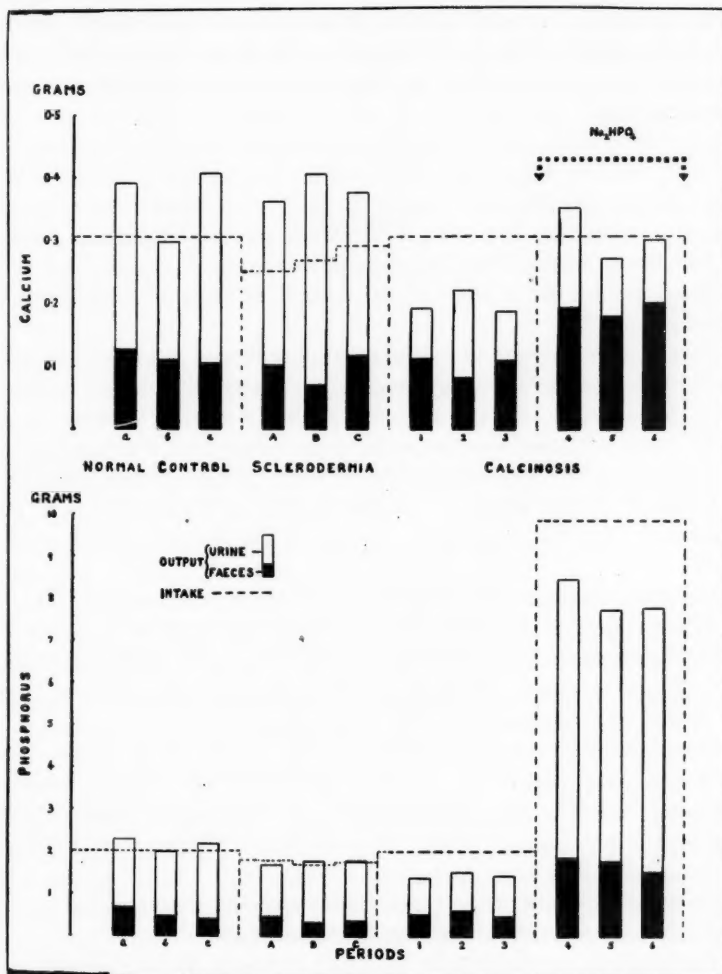


FIG. 3. The metabolism of calcium and phosphorus, in a normal control, a case of sclerodermia, and one of calcinosis. Each figure represents the output per three-day period, while the intake is shown by the corresponding level of the dotted line. On the right is shown the effect of the ingestion of alkaline sodium phosphate in the case of calcinosis.

in the subcutaneous concretions, it was apparent that mobility of both knee- and hip-joints had slightly increased. Radiological examination at this stage as compared with previous examinations showed a considerable reduction of the deposits in the regions of the thighs and buttocks, without

change in the condition of the bones. The patient was then discharged to continue the diet and therapy at home. She returned a month later for examination; there was then a demonstrable improvement of gait, and it was, perhaps, significant that for the first time the level of serum calcium was within normal limits. After more than a year's treatment on these lines still further improvement was demonstrable clinically, and by radiological examination (Plate 19, Fig. 2); moreover, the blood chemistry was then normal.

### *Summary*

1. A review is made of the literature of calcinosis.
2. Investigations of a case of calcinosis, and one of scleroderma are reported.
3. On a diet inadequate in calcium and phosphorus, but otherwise normal, the case of scleroderma gave evidence of an essentially normal metabolism of these elements; the case of calcinosis showed a marked tendency to retain both calcium and phosphorus following a probably normal absorption.
4. The case of calcinosis exhibited over a long period of time pathologically high levels of serum calcium, plasma inorganic phosphate, and plasma phosphatase. In this respect the values in the case of scleroderma were normal.
5. Disodium hydrogen phosphate restored the calcium metabolism to an approximate equality of intake and output in the case of calcinosis. Accompanying this there was a fall in the level of calcium and phosphatase in the blood, and a rise in the level of phosphorus. Indications of improvement in the patient's condition also occurred.
6. Chemical study of a calcareous nodule, removed at biopsy, showed that it consisted mainly of calcium phosphate and calcium carbonate. Quantitative analysis demonstrated that the ratio of residual calcium to phosphorus approximated closely to those found by previous investigators for normal bone, and for pathological calcification.
7. Histological study of the concretions suggested that the initial deposition of calcium occurred in degenerate fibrous tissue.
8. Radiological investigations disclosed the considerable extent of the disease, and showed also a pronounced generalized decalcification of the skeleton as compared with a normal control. Epiphyseal union was also advanced. During the period of observation of this patient, no change in bone density was observed, although definite reduction in the extent of the pathological calcification occurred.
9. The above results suggest that in calcinosis a local tissue change, of as yet undetermined kind, results in localized fibrous tissue damage, and that when calcification occurs in these areas there may be an accompanying abnormality of calcium and phosphorus metabolism. The type of lesion

present in scleroderma does not necessarily produce changes which result in abnormality in the metabolism of calcium and phosphorus.

It is a pleasure to acknowledge the debt of gratitude we owe to many colleagues in carrying out this investigation. We are greatly indebted to Dr. Donald Hunter of the London Hospital for his kind advice and assistance in the methods of study of the metabolism of these patients. Our thanks are also due to Dr. H. C. Gage and Dr. W. D. Newcomb, who gave much of their time and work, and submitted respectively the radiological and pathological reports. Finally, to Professor F. S. Langmead and Dr. T. C. Hunt, under whose care these patients were, we are indebted, not only for making this work possible, but also for their kindly and invaluable advice and help throughout.

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TABLE I

Period 3 days.	Date.	Calcium balance (gm.).			Phosphorus balance (gm.).			Comments.
		Output.		Intake.	Output.		Intake.	
1	2.3.32	U = 0.081			U = 0.886			Case. E. G. ♀. Aged 15. Diagnosis: <i>calcinosis universalis</i> . Diet: Total calories = 1502 per diem Ca, P, very low. Therapy: nil.
	to 4.3.32	F = 0.112	T = 0.193	0.306	F = 0.504	T = 1.390	2.016	
2	5.3.32	U = 0.140			U = 0.904			
	to 7.3.32	F = 0.082	T = 0.222	0.306	F = 0.619	T = 1.523	2.016	
3	8.3.32	U = 0.077			U = 0.940			
	to 10.3.32	F = 0.110	T = 0.187	0.306	F = 0.497	T = 1.437	2.016	
4	17.6.32	U = 0.158			U = 6.577			
	to 19.6.32	F = 0.195	T = 0.353	0.306	F = 1.873	T = 8.450	9.846	
5	20.6.32	U = 0.091			U = 5.944			
	to 22.6.32	F = 0.181	T = 0.272	0.306	F = 1.792	T = 7.736	9.846	
6	23.6.32	U = 0.099			U = 6.071			
	to 25.6.32	F = 0.202	T = 0.301	0.306	F = 1.546	T = 7.517	9.846	

Case: same. Diagnosis: same. Diet: same. Therapy:  $\text{Na}_2\text{HPO}_4$  3i t.d.s.

TABLE II

Period 3 days.	Date.	Calcium balance (grm.).			Phosphorus balance (grm.).			Comments.		
		Output.	Intake.	Balance.	Output.	Intake.	Balance.			
a	15.7.32	U = 0.263	T = 0.391	0.306	-0.085	U = 1.607	T = 2.290	2.016	-0.174	Case. L. R. ♀. Aged 15 (control). Diagnosis: mild chronic non-active rheu- matic carditis. Diet: same. Therapy: nil.
	17.7.32	F = 0.128				F = 0.683				
b	18.7.32	U = 0.187	T = 0.298	0.306	+0.008	U = 1.526	T = 1.998	2.016	+0.018	
	20.7.32	F = 0.111				F = 0.472				
c	21.7.32	U = 0.303	T = 0.409	0.306	-0.103	U = 1.788	T = 2.191	2.016	-0.175	
	23.7.32	F = 0.106				F = 0.403				
A	19.6.32	U = 0.259	T = 0.362	0.257	-0.105	U = 1.210	T = 1.672	1.719	+0.047	Case. L. F. ♀. Aged 41. Diagnosis: <i>scleroderma</i> . Diet: same. Therapy: nil.
	21.6.32	F = 0.103				F = 0.462				
B	22.6.32	U = 0.327	T = 0.406	0.278	-0.128	U = 1.433	T = 1.758	1.696	-0.062	
	24.6.32	F = 0.079				F = 0.325				
C	25.6.32	U = 0.258	T = 0.376	0.292	-0.084	U = 1.413	T = 1.770	1.756	-0.014	
	27.6.32	F = 0.118				F = 0.357				

TABLE III

(Diet values given as grms. or calories per diem; each period lasted three days.)

Patient.	Period.	Date.	Average weight.	Carbohydrates (gm.).	Protein (gm.).	Fat (gm.).	Calcium (gm.).	Phosphorus (gm.).	Calories.	Therapy.
E. G. (calcinosis)	1, 2, & 3	2.3.32	105.5 lb.	218	54	46	0.102	0.672	1502	Nil
		to 10.3.32								
E. G.	4, 5, & 6	17.6.32	100 lb.	218	54	46	0.102	3.282	1502	$\text{Na}_2\text{HPO}_4$
		to 25.6.32								
L. R. (control)	a, b, & c	15.7.32	106 lb.	218	54	46	0.102	0.672	1502	Nil
		to 23.7.32								
L. F. (scleroderma)	A	19.6.32	82 lb.	161.6	33.5	42.5	0.086	0.573	1162.9	Nil
		to 21.6.32								
	B	22.6.32	82 lb.	218	29	41	0.093	0.565	1357	Nil
		to 24.6.32								
	C	25.6.32	81.5 lb.	218	29	41	0.097	0.585	1357	Nil
		to 27.6.32								

TABLE IV. *Blood Chemistry*

Date.	E. G. (calcinosis).			Comments.	L. R. (Control).			L. F. (sclerodermia).		
	Serum Ca.	Plasma inorg. P.	Plasma phosphatase.		Serum Ca.	Plasma inorg. P.	Plasma phosphatase.	Serum Ca.	Plasma inorg. P.	Plasma phosphatase.
Nov. 1931	12.2	7.67	—	At admission	—	—	—	—	—	—
Jan. 1932	13.1	5.29	—	With normal hospital diet	—	—	—	—	—	—
March 1932	13.3	5.63	0.331	Special diet period 2	—	—	—	—	—	—
April 1932	13.7	6.10	0.402	Special diet	—	—	—	—	—	—
June 1932	11.3	8.62	0.175	Special diet therapy period 5	—	—	—	† 10.9	3.32	0.180
July 1932	—	—	—	Special diet therapy	* 9.6	4.76	0.162	—	—	—
Aug. 1932	10.5	5.79	—	Special diet therapy	—	—	—	—	—	—
Nov. 1933	11.56	4.20	0.200	Special diet therapy	—	—	—	—	—	—

(Serum calcium, and plasma inorganic phosphate in mgm. per 100 c.c., plasma phosphatase in units (Kay))

\* Period (a) † Period (b)





The case of calcinosis, showing superficial calcareous deposits, some ulcerated, about the knees, elbows, forearms, and fingers. The scars of two recent biopsy wounds are to be seen on the left forearm



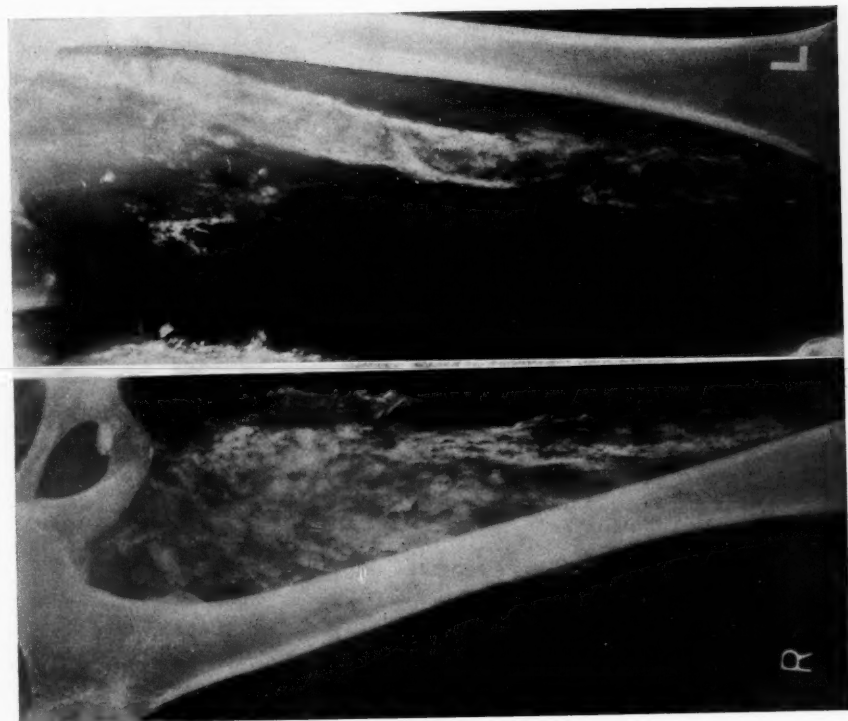


FIG. 1. Calcinosis. Deposits in the thighs of the patient, for the most part within and around muscles. (Before therapy)

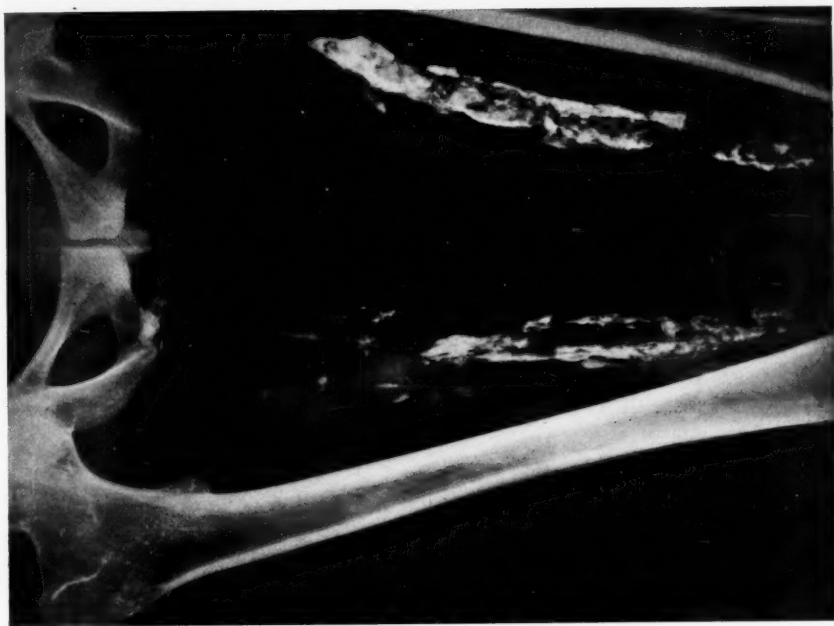
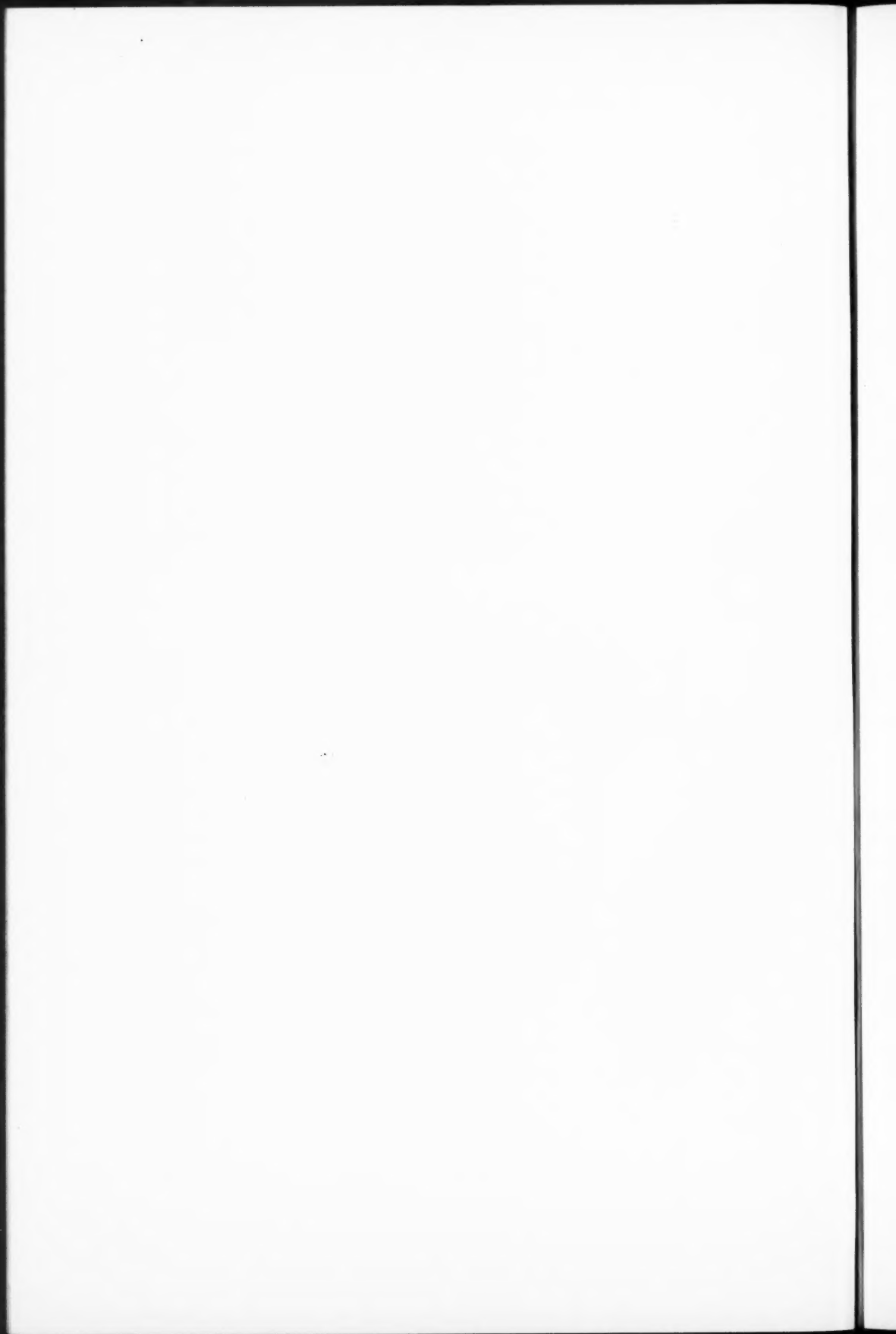


FIG. 2. Calcinosis. Deposits in the thighs (Nov. 1933) after more than one year's therapy with alkaline sodium phosphate



## A STATISTICAL ANALYSIS OF 389 FRACTIONAL TEST MEALS

WITH SPECIAL REFERENCE TO DUODENAL REGURGITATION<sup>1</sup>

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THIS investigation was undertaken in an attempt to throw light upon two points of great importance in the interpretation of fractional test meals, namely, the role of duodenal regurgitation and the relation between hyperacidity and pyloric function. The current views on these topics which have arisen out of the researches of Boldyreff (2), Rehfuess (24), Bennett (3), Ryle (25), Bolton and Goodhart (6), and others, may be roughly summarized as follows:—

1. In the normal individual duodenal regurgitation occurs towards the end of the test meal and is responsible for the fall of acidity which often takes place at that time.

2. 'Hyperacidity' or the 'climbing curve' is usually due to interference with pyloric relaxation, either by organic or reflex causes. This results in failure of duodenal regurgitation and undue retention of the products of digestion.

These views are not, however, universally held, and have been vigorously attacked during the last few years. Baird, Campbell, and Hern (2) appear to have been the first to doubt the theory of duodenal regurgitation, and later MacLean and Griffiths (18) in a series of papers, claim to have disproved its importance as a factor in the regulation of gastric acidity, which they believe to be controlled by the secretion of a natural fluid by the stomach. This earlier work will not be considered in detail as it has recently been reviewed by Goldberg (13). More recently Shay *et al.* (26) have used brom-sulphonephthalein as an index of duodenal regurgitation in an extremely ingenious manner. They first injected the dye intravenously into a number of patients, and determined by intubation the concentration of dye reached in the duodenum at definite intervals after injection; test meals were later administered to the same patients after the same injection of dye, so that by estimation of dye in the stomach contents the amount of regurgitation could be assessed. In all their cases the amount of regurgitation proved to be quite negligible in comparison with the acid concentration in the stomach.

<sup>1</sup> Received January 6, 1934.

Again, while the frequent occurrence of hyperacidity in peptic ulcer is generally accepted, two different explanations of this association are given. According to some, the ulcer causes pylorospasm, which increases acidity as explained above, whilst Hurst (14) regards the hyperacidity as being a part of the 'hypersthenic gastric diathesis', which is an inborn condition, so that the hyperacidity precedes the ulcer, and is merely a predisposing cause of the ulcer. It is interesting to note that this diathesis is associated with a rapidly emptying stomach which is in direct opposition to the alternative theory.

Further evidence on this point is forthcoming from a different source. Pollard (22), working with the histamine test meal, has shown in a large number of cases exactly the same relationship between ulcer and hyperacidity (which he does not however recognize as a clinical entity) as had been shown previously with the gruel meal. Since in the histamine test no meal is given, pure gastric juice is examined and duodenal regurgitation is virtually excluded, these results are strongly in support of what may be called the secretory as opposed to the mechanical theory of hyperacidity.

In the present paper an attempt is made to correlate the type of curve with pyloric function by examining with special care the occurrence of bile, the emptying time, and the volume of residue at two hours. The assumptions are made that the emptying time and two-hour residue are an index of the tone of the pyloric sphincter, and that bile is an index of duodenal regurgitation. The implications of the emptying time and volume of residue are sufficiently obvious, but the question of bile merits some further discussion.

It has long been known that bile is frequently present in samples withdrawn during a fractional test meal. This was part of the evidence on which the theory of duodenal regurgitation was based (Boldyreff (4), Rehfuess (24), Bennett and Ryle (3 a), Bolton and Goodhart (6). It has also been pointed out that it is frequently absent from 'normal' curves (i.e. curves showing a peak with a subsequent fall of acidity) or appears in them at such a time as to be an unlikely cause of the fall. (MacLean (17), Baird *et al.* (2), Crohn (9)). This is a valid criticism of the theory, but has been discounted by Bolton (5) on the ground that pancreatic juice may regurgitate without bile.

Now while proof of this dissociated regurgitation has been given by many observations on gastric trypsin (Spencer, Meyer, Rehfuess, and Hawk (27), Medes and Wright (19)), we must remember that regurgitation in the present connexion means regurgitation as a factor in the neutralization of gastric acidity, and there is no proof that dissociated regurgitation ever occurs to this extent. It has been pointed out by Shay *et al.* (26) that earlier observations such as those on gastric trypsin entirely failed to correlate with the concentration of the test substance—trypsin, diastase, bile—in the stomach and duodenum; a trace of trypsin in the stomach may well correspond to a trivial amount of regurgitation, for the duodenal concentra-

tion is probably very high. In the experiments of Baird, Campbell, and Hern (2) in which the stomach and duodenum were simultaneously intubated, bile appeared in the duodenal tube at one minute after the meal in every case, and persisted to the end. Unless this experience is unusual, it must surely be impossible for significant regurgitation to occur without bile appearing in the test meal.

These considerations appear to me to justify the use of bile as an index of duodenal regurgitation in all cases where the absence of biliary obstruction can be assumed, i.e. in the very great majority. But even granting the occasional occurrence of dissociated regurgitation the principle may still be applied to a large number of cases. The conclusion seems inescapable that, if in two series of cases more regurgitation is occurring in one than in the other, that one must show a greater incidence of bile, for there is every reason to suppose that the occasional cases of dissociated regurgitation will be evenly distributed between the two series. The best estimate of the incidence of bile has been taken as the percentage of specimens containing bile rather than the percentage of cases, since the former obviously gives more precise information by taking into account the amount of bile in each meal with greater accuracy.

Special attention has also been paid to the exact moment of appearance of the bile in relation to the fall in acidity where this occurs. This is an important point which, although frequently commented upon, has apparently received little accurate attention beyond a remark by Baird, Campbell, and Hern (2) to the effect that 'curiously enough in half the cases with a well-marked peak bile is not present at any time; in only one quarter does bile appear at such a time that it seems the probable cause of the fall in acid and resulting peak'.

#### *Method of Study*

The material presented consists of 454 consecutive fractional test meals performed in the Courtauld Institute of Biochemistry, The Middlesex Hospital, London, on a miscellaneous collection of patients during 1931-3. The patients were referred to the Institute from the wards and out-patient departments, and, if out-patients, they were given written instructions concerning their preparation. This consists of a light meal at 8 p.m., a charcoal biscuit at 10 p.m., and then complete starvation until the test is performed the next morning. The meal was of the fractional type, the technique described by Beaumont and Dodds (2a) being strictly adhered to. This includes removal of the resting juice, a careful washing out of the stomach with warm water until the rinsing fluid is returned clear, the administration of one pint of oatmeal gruel, and removal of specimens every quarter hour for two hours. At two hours the stomach is completely emptied and the volume of the residue noted. All the tests were performed

by medically qualified assistants with special experience in this work, who personally collected and analysed the specimens.

No attempt has been made to correlate the findings with the diagnosis, except to exclude cases of gastro-enterostomy, organic pyloric stenosis (resting juice of more than 150 c.c. and containing charcoal) and gross gastric deformity (resting juice of normal volume, but containing charcoal and showing such evidence of stagnation as blood plus foulness).

The curves were first divided up into the following classes illustrated diagrammatically in Table I:

1. *Anacidity*. 74 cases. No free acid to Toepfer's reagent.
2. *Late secretion*. 13 cases. No secretion of free acid during the first hour.
3. *Rising curves*. 58 cases. Showing a continuous rise of acidity up to a value of free acid not exceeding 45 c.c. N/10 HCl per cent. This is the upper limit of Bennett and Ryle's (3*a*) normal standard.
4. *Low plateau*. 76 cases. Showing a more or less well-defined plateau, free acid not exceeding 45.
5. *High plateau*. 21 cases. Showing a plateau with free acid exceeding 45.
6. *Climbing curve*. 45 cases. Showing a continuous rise to a value of free acid exceeding 45.
7. *Peak curves*. 102 cases. Showing a definite peak with a subsequent fall in acidity of at least 10 units, with the proviso that the fall is not confined to the last  $\frac{1}{4}$ -hour before the stomach empties itself. A fall in these circumstances when the stomach contains only a small volume of fluid, is likely to be due to accidental contamination with saliva.
  - 7*a*. *Fall corresponds to bile*. 19 cases. The fall has been said to correspond to bile if bile was present at all while the actual fall was occurring. If the bile occurred wholly either before or after the fall, or was absent altogether, the curve was classified as—
  - 7*b*. *Fall does not correspond to bile*. 83 cases.
8. *Bile in more than two specimens* (excluding the resting juice). 61 cases.
9. *Not classified*. 52 cases. On account of pyloric stenosis, gastro-enterostomy, gross deformity of stomach, incompleteness of record, much haemorrhage during meal, and evidence of incomplete emptying of stomach before test ( $\frac{1}{4}$ -hour specimen of high acidity).

Naturally the classification of border-line cases must be to some extent a matter of opinion, but great care was taken to avoid any bias by deciding first upon the form of the curve, before its other characteristics had been noted; it must be emphasized that this classification depended entirely upon the shape of the curve and not on any other factor except the acidity. The definition of the 'climbing curve' presented some difficulty, for there does not seem to be any accurate definition of what constitutes this much discussed type. Thus Roholm (23) uses the term for a curve obtained after

the starch reaction has disappeared, whilst most other writers consider only that part of the curve where starch is present. The above definition appeared to be the simplest which would serve as a reasonable basis for selection.

The following details were then noted on each curve. (1) Volume of resting juice, presence of charcoal, blood, or foulness. (2) The highest free acidity reached. (3) The emptying time, as shown by the end of the starch reaction or the failure to obtain further specimens, whichever occurred first. (4) Volume of residue at two hours, if any. (5) Total number of specimens withdrawn up to the emptying time, excluding the resting juice. (6) Number of such specimens which contained bile. (7) Number of such specimens which contained mucus. (8) Presence or absence of gross haemorrhage during the meal.

The emptying times and volumes of residue were then averaged in each class and the incidence of bile and mucus was expressed (*a*) as a percentage of specimens, and (*b*) as a percentage of cases showing bile and mucus respectively in one or more specimens. The superiority of (*a*) over (*b*) has already been remarked upon. Both the emptying time and the residue were averaged over the total number of cases in each class, although of course some cases had no residue and some were not empty at two hours; thus the emptying time of cases having a residue at two hours was taken as two hours. This was necessary in order to obtain comparable results.

These figures form the basis of an attempt to correlate the type of curve with pyloric function, as explained above. The percentage of mucus was also studied as a matter of completeness.

Now the accuracy of these means and percentages is affected by *errors of random sampling*. This means that we should not expect the same analysis of a similar 389 cases to give absolutely identical results. Consequently we cannot say from a casual inspection of the figures that, for example, the anacid class empties more rapidly than the climbing, or that the peak class contains more bile than the climbing. Analysis has in fact shown that while the first statement is justified, the second is not. In order to draw any such inferences we require to know the error of random sampling in each class. This is readily calculated by established statistical methods, the application of which will now be described.

#### *Statistical Analysis of Results.*

*Volume of residue and emptying time.* The standard error of the mean was calculated in the usual way by squaring the differences from the mean. If  $\bar{x}$  is the mean of  $n$  values of  $x$ , the standard error of the mean is estimated by the expression  $\pm \sqrt{\frac{S.(x - \bar{x})^2}{n(n-1)}}$ . Even if the actual values of  $x$  are not normally distributed, the means of reasonably large samples will be sufficiently

nearly normally distributed to use the normal curve in calculating the odds against a given difference occurring by chance (Fisher (10)).

The application of the standard error to the difference of two means, which is the most important point in the present analysis, is as follows:

If  $\bar{x}_1 \pm \sigma_1$ ,  $\bar{x}_2 \pm \sigma_2$  are the means and standard errors of two independent varieties, the standard error of the difference is  $(\bar{x}_1 - \bar{x}_2) \pm \sqrt{\sigma_1^2 + \sigma_2^2}$ .

This difference is only considered to be significant if it exceeds twice its standard error, which will only happen by chance about 5 times out of 100. If it does not exceed twice its standard error, we must conclude that there is no evidence to show that the two means are in fact different.

The significance of the difference may also be tested in a more rigid manner, which is valid even for small samples. This consists in the

calculation of a value  $t = \frac{\bar{x}_1 - \bar{x}_2}{S} \sqrt{\frac{n_1 + 1)(n_2 + 1)}{n_1 + n_2 + 2}}$  where  $S^2$  is an unbiased estimate of the variance. The value of  $t$  which, for a given value of  $n = n_1 + n_2$ , will only be exceeded by chance in 5 per cent. of cases, is then found from a table. When  $t$  exceeds this value, the difference is considered significant (Fisher (10)). This method has been applied to several differences of means of both residues and emptying times in cases where the first method showed standard errors near the limit of significance, and in every case the two methods agreed well. It is evident, therefore, that the methods appropriate to large samples are applicable without serious error. An example of these calculations is given in Table II.

*Percentage of bile and mucus in specimens and cases.* These figures differ from those discussed above in two respects. Firstly, they are derived from figures which are whole numbers, for a specimen or case is said either to contain bile or not to contain bile. Secondly, the mean percentage gives information both about specimens containing bile and about those not containing bile, e.g., if 13 per cent. contain bile, then 87 per cent. do not. This is equivalent to saying that the probability that any one specimen will contain bile is 0.13 and the probability that it will not is  $(1 - 0.13) = 0.87$ , so that the appropriate treatment is that of the Binomial distribution.

If  $n$  = number of specimens or cases,

$p$  = percentage of specimens containing (say) bile,

$q$  =  $(100 - p)$  percentage not containing bile,

the standard error of  $p$  is  $\sqrt{\frac{pq}{n}}$ . This formula will apply equally to the percentage of cases.

The difference of two percentages may then be treated exactly as above.

In doubtful cases an alternative method was applied which is valid except for very small samples or for values of  $p$  or  $q$  very close to 100 per cent. This consists in assuming that the two percentages, whose difference is required, are drawn from the same population, the characteristics of which

are estimated by summation (vide Table III). The variance of each is then  $\frac{PQ}{n}$  where  $n$  refers to the sample concerned but  $P$  and  $Q$  refer to the hypothetical common population.

The two standard errors are then

$$\sqrt{\frac{PQ}{n_1}} \quad \sqrt{\frac{PQ}{n_2}}$$

and the standard error of the difference  $(p_1 - p_2)$  is

$$\sqrt{PQ \left( \frac{1}{n_1} + \frac{1}{n_2} \right)}$$

which may be treated as a normal deviate even for comparatively small values of  $n$ . Thus, if  $(p_1 - p_2)$  exceeds twice its standard error, the two samples were not drawn from the same population, i.e. the difference is significant.

The results obtained by this method agreed well with those given by the previous one, although revealing a slightly greater error in the difference in each case. An example of these calculations is given in Table III.

### Results

Inspection of Table IV reveals at once a most striking and unexpected uniformity in the characteristics of the different types of curves, the significant variations being very few. This point is further illustrated in Figs. 2 to 7, in which some of the means are plotted together with their standard errors. The horizontal lines represent the means, and the vertical lines the standard errors. It should be noted that while it is correct to say that if the standard error lines overlap no significant difference exists, the converse is not true. For example, the percentage of bile in specimens in anacid and climbing curves is not a significant difference. The only correct test consists in the application of the formulae already quoted, which leads to the results given below.

At the risk of some repetition the reader must again be cautioned against the fallacy of basing conclusions upon differences which are within the limits of the errors of random sampling. The position is that such results signify not so much a doubt as to the magnitude of the difference, but the complete failure to demonstrate the existence of any difference whatsoever. It is therefore only possible to draw sound inferences from the data by the rigid application of statistical principles, for most of the differences are small and it is quite impossible to decide by inspection whether they are significant or not.

The anacid and rising curves show a more rapid emptying time than most of the others, although the difference between rising and climbing is not significant. If anacid and rising curves be excluded, there is no significant variation among the remainder.

Only anacid and rising curves differ significantly from the general mean volume of residue. No variations were seen among the remainder.

No significant variations were found in the percentage of bile in the specimens except where the classification depends upon the presence of bile.

The difference between peak and rising curves is the only significant one in the percentage of bile in cases.

As to the percentage of mucus in the specimens the curves are divided into three classes, the members of which show no individual variations, except that the late secretion occupies an intermediate position possibly owing to its large error. (i) Anacid (0). Late secretion (15.2). (ii) Low plateau (26.4). Peak (35.8). (iii) Rising (31.0). High plateau (56.1). Climbing (66.1).

The figures in brackets represent the average highest free acidity, which is referred to below.

Anacid curves exceed the general mean in the percentage of mucus in cases, otherwise no variations are apparent.

Classification according to the amount of bile does not reveal any difference in the curves containing higher percentage of bile. (See also below and Table IV.)

The results in general may be considered as positive and negative.

*Positive results.* Anacid curves show a rapid emptying time and a small residue. This is, of course, a well-recognized fact, although the explanation is at present obscure.

Rising curves show a rapid emptying time with a large residue. It is possible that the former is to some extent a product of the method of classification—the curves have been labelled 'rising' because the stomach emptied before an acidity higher than 45 could be attained—but no reason can be suggested by the writer for the latter finding.

The distribution of mucus is of some interest, although one feels that the original observations on the presence or absence of mucus are so frequently a matter of opinion that definite results are rather surprising. The increased mucus in anacidity finds a ready explanation on account of the association of gastritis with this condition, and in general the amount of mucus appears to bear a roughly reverse relation to the height of acidity reached. To illustrate this point the average highest free acidity is placed in brackets after the name on the above scheme. A similar relationship has been noted clinically by Ryle (25), Crohn (9), and others.

*Negative results.* It is these which are of special importance in their bearing on the theories which have been referred to above.

There is complete lack of correlation between the incidence of bile and the much discussed fall of acidity. Thus out of 102 cases showing a peak, only in 19 does the appearance of bile correspond at all to the fall, and in 57 bile is absent throughout. Moreover, the percentage of bile in specimens, which is probably the most accurate index of duodenal regurgitation, is not significantly different in the peak class from that of the climbing or high

plateau classes, which are commonly supposed to arise by the very opposite process of pyloric spasm or achalasia. In the group labelled 'fall corresponds to bile' a very high percentage of bile is present (47.3 per cent. of specimens). This probably means that the fall was attributed to bile because, as so many specimens contained bile, it could hardly fail to be present during the actual fall. There appears to be no special reason to ascribe the fall to duodenal regurgitation, even in these few (19) cases.

An alternative way of testing this relationship consists in examining the incidence of the various types of curve among the cases containing bile in more than two specimens. These cases contain 62.2 per cent. of bile in specimens, so that it should be instructive to compare them with those in which bile is completely absent. This has been done in Table IV.

It will be seen that the distribution of types is almost the same in the two classes, and there are evidently no significant differences to be found. The greatest difference occurs in the two peak groups, but this is well within the limits of sampling errors, for the difference is 8.70 and its standard error (computed as in Table III, method II) is  $\pm 6.10$ .

It has been shown above that the residue and emptying time of these curves are similar to those of the whole series, so that we arrive now at the remarkable result that a series of curves in which nearly two-thirds of the specimens contain bile does not appear to differ in any way from a parallel series in which bile is completely absent. It is a reasonable conclusion that the presence or absence of bile can have had little effect upon the character of any of these curves, and it is but a short step to substitute 'duodenal regurgitation' for 'bile'.

Evidence of pyloric influence may also be sought in a comparison of the emptying times and two-hour residues of the different types of curves. Here again we find no differences, except in the anacid and rising curves. Thus the climbing and high plateau curves do not differ significantly from the peak curves, although an opposite condition of the pylorus is commonly postulated in the two groups. It may be noted also that the hyperacid curves do not show the rapid emptying time which we should expect as a part of the 'hypersthenic gastric diathesis'.

### *Discussion*

It will be seen that the results of the analysis give no support to the two theories which it was designed to test. It is extremely unlikely that such a series of cases would fail to show any trace of pyloric influence in the sense demanded if the supposed relationships have any foundation in fact. The failure to find indications of any difference in the action of the pylorus in the various types of curve (excepting in anacidity) is therefore a very strong argument against the theory of duodenal regurgitation and its role in the prevention of hyperacidity.

It is not proposed to give an account here of the numerous objections which have previously been raised to it, for the subject has been recently reviewed by Goldberg (13) who lays stress upon the intragastric regulation of acidity, and by Shay *et al.* (26) who are frankly opposed to the theory of duodenal regurgitation. It is, however, MacLean and Griffiths (18) who first proposed the rejection of this theory, and the results reported in the present paper are in perfect agreement with MacLean's contention (17) that 'duodenal regurgitation, when it occurs, is an accident . . . it is in no way connected with the reduction of hydrochloric acid and the associated rise of neutral chloride which occurs during digestion'. It remains to point out some of the consequences which will follow this rejection, if indeed it becomes generally accepted.

In the first place, if duodenal regurgitation does not cause the fall of acidity in the 'normal' or peak curve, what does? Excluding the swallowing of saliva which may possibly account for a few cases, there appear to be three possibilities.

1. *Absorption of the acid by the stomach* has been suggested by Shay *et al.* (26) as a cause of the rapid reduction of acidity which they observed after introducing acid solutions into the stomach. For example, in one experiment a meal of 200 c.c. equivalent to 140 c.c. N/10 HCl became in five minutes 230 c.c., equivalent to 100 c.c. N/10 HCl. However, since the more likely possibility that some of the acid had passed through the pylorus, to be replaced by a less acid gastric secretion, was not apparently considered, this can hardly be regarded as proved. In any case, it seems improbable that during an ordinary meal the stomach would both secrete and absorb acid, so that we may dismiss this for the present.

2. *Secretion of a neutral fluid by the stomach* is the explanation of MacLean and Griffiths (18), and they advanced good evidence for believing that this actually occurred in many of their curves. There are, however, reasons for regarding this as a special case of the third possibility.

3. *Secretion of an alkaline fluid by the stomach.* This appears to have been suggested first by Baird, Campbell, and Hern (2), whose important paper enjoys the unique distinction of being freely quoted both in support of and against the theory of duodenal regurgitation. Actually they wrote of the alkaline pyloric mucus as the most important neutralizing agent in their own cases, but admitted that duodenal regurgitation might be of importance in others.

The fact that neutralization as distinct from dilution occurs in the stomach has been shown by Norris and Apperly (21) who performed test meals using a neutral substance such as urea or glucose as a dilution indicator. The meals consisted of solutions of hydrochloric acid and they were able to divide them into three classes by observing the relation of the urea curve to the acid curve. If the two concentrations fell in a parallel fashion, simple dilution must have occurred; neutralization was indicated by a more steeply falling acid curve, and secretion of acid by a more steeply falling urea curve.

This interesting method produced evidence of neutralization in 24 out of 57 cases in which acid of strength about N/10 was placed in the stomach. Norris and Apperly ascribed their results to duodenal regurgitation, and while this interpretation may now be questioned, they remain as a rather convincing demonstration of intragastric neutralization.

There are in fact many curves which do not easily admit of any other explanation. For example, take Fig. 8 which is specially selected from the present series but is by no means exceptional. Assuming that the volume of stomach contents at  $1\frac{1}{2}$  hours was not less than that of the residue, 105 c.c., to reduce this from a free acidity of 25 to 0 would require the equivalent of  $\frac{25 \times 105}{100} = 26$  c.c. N/10 NaOH. It is of course impossible to calculate accurately how much neutral fluid would be required to effect the same change owing to the unknown buffering power, but an approximation may be made by calculating the volume of water required to change 105 c.c. of pure hydrochloric acid of equivalent strength (0.025 N) to the end point of Toepfer's reagent (about pH 0.4). This works out at  $\frac{0.025}{0.0001} \times 105 = 26$  litres.

Even making all allowance for the acid which may have left the stomach during the last half hour, this value is so high as to suggest that dilution is not an adequate explanation of the curve. The complete absence of bile may be emphasized.

What then is the nature of this alkaline secretion? It must be admitted that there is at present no general agreement on this question, which is perhaps because most of the direct experimental work must perforce be done on animals, and the results are not always easy to reconcile with those obtained with human beings. There are reasons for associating the neutralizing agent both with gastric mucus and with the secretion from the pyloric portion of the stomach, which is possibly the same thing. The notion of 'alkaline pyloric mucus' is an old one, dating at least from Klemensiewicz (16) in 1875, and has recently been put upon a more quantitative basis by the work of Gamble and McIver (12). Working with the fundic and pyloric pouches of the Pawlow type in cats, they showed that the pyloric secretion contained fixed base in excess of chlorine, so as to be equivalent to an alkali of strength about 0.01 N. This does not imply that the secretion is so alkaline in reaction, for it is well buffered; according to the earlier work of Ivy and Oyama (15) it consists principally of mucus and the pH does not exceed 7.5.

A general study of gastric mucus has also been made by numerous workers, among whom may be mentioned Bonis (8), Mitchell (20), Bolton and Goodhart (7), and Fogelson (11). The first two of these showed that the buffering power was due principally to the sodium bicarbonate, since it was much reduced by dialysis. Bolton and Goodhart give a value for the mucus secretion of the cat which corresponds to an alkalinity of 0.039 N,

but they do not credit the secretion with the power to neutralize appreciable quantities of acid until the stomach is nearly empty. It is, however, a far cry from these experiments on decerebrate cats under pilocarpine stimulation to the human test meal. Fogelson prepares solid mucin from hogs' stomachs which is capable of neutralizing considerable amounts of hydrochloric acid. This normal mucus must be carefully distinguished from the pathological mucus upon which attention is apt to be focused in test meals, the relation of which to gastric neutralization is even more doubtful.

To return now to the original problem we must seek to explain the peak curve by a change in the character of gastric secretion during the meal. The first rise in acidity corresponds to the most acid secretion, which probably comes from the fundus; towards the end of the meal an alkaline secretion begins to appear, perhaps from the pyloric region, or perhaps from the mucoid glands as suggested by Babkin (1). A fall will occur if the combined acid and alkaline secretions at any moment represents a concentration of acid less than that of the stomach contents at the same moment. A further relative increase in the alkaline secretion will produce the neutral diluting fluid of MacLean, and a still further increase will effect actual neutralization of stomach contents; thus any of the three types of curves described by Norris and Apperly could be produced by a purely intragastric mechanism. This scheme may be considered as an extension of MacLean's and Griffiths's theory of automatic regulation of gastric acidity, but it is not intended to include any hypothesis either as to the nervous mechanism involved, or of the regulation to any definite pH level. It represents merely a possible explanation of the various types of peak curve without recourse to duodenal regurgitation.

The second point concerns the aetiology of hyperacidity. If this is not in general due to pylorospasm or pyloric achalasia, we are more or less driven to accept the alternative theory of Hurst (14), which is so well supported by recent work with the histamine test meal (Polland (22)). This appears now to provide the only way of explaining the frequency of hyperacidity in peptic ulcer, unless indeed we care to assume that the ulcer causes a hypersecretion of acid. But many arguments have been advanced against this by Hurst, perhaps his most convincing being that the level of the acid in the test meal actually rises as a result of treatment in cases of ulcer, so that higher values are found after the ulcer has healed. We may note in passing the interesting suggestion of Roholm (23), that the climbing curve is due to a gastritis localized to the pyloric region. While this fits in well with the work on alkaline pyloric secretion which has been quoted, it lacks at present any direct experimental evidence.

A further point arises with reference to the 'hypersthenic gastric diathesis'. It has been mentioned above that the hyperacid curves do not show a rapid emptying time, so that at least one of the criteria of this diathesis has not been fulfilled in these patients. This raises the question of whether the association of hypersecretion with a particular type of stomach is in fact so

constant as has been generally assumed since the work of Campbell and Conybeare (8a). Further observation on this matter would be very desirable.

The acceptance of these conclusions will also necessitate the revision of our views on the significance of the climbing curve. It would appear to be a sign of hypersecretion and not of pyloric irritation, so that the only localizing help which may be expected from the fractional test meal in the diagnosis of juxtapyloric lesions will be that of detecting pyloric stenosis, early or late. Hyperacidity will still be of some interest, but its value as a diagnostic sign will be greatly reduced.

### *Summary*

1. A statistical analysis has been made of the emptying time, volume of residue at two hours, and of the incidence of bile and mucus in 389 fractional test meals. These were divided into seven main classes for this purpose.

2. There are very few significant differences between the various types with two exceptions: (a) The anacid curves showed a more rapid emptying rate and a smaller two-hour residue. (b) The distribution of mucus was in roughly inverse proportion to the height of the acidity.

3. There was no evidence of increased duodenal regurgitation in the peak curves. Some of the evidence for an intragastric mechanism of the fall in acidity has been reviewed and a provisional hypothesis suggested.

4. Curves containing a high proportion of bile did not show any difference from those in which bile was completely absent, either in type incidence or motility.

5. There was no evidence of pyloric spasm or achalasia in the curves showing hyperacidity. Alternative theories of the production of hyperacidity have been mentioned.

6. There was no evidence of rapid emptying in the hyperacid curves. The bearing of this observation on the conception of the hypersthenic gastric diathesis has been discussed.

7. If these conclusions be accepted the climbing curve can no longer be considered a sign of pyloric irritation.

It is a pleasure to express my thanks to Professor E. C. Dodds for permission to consult the files of the Courtauld Institute of Biochemistry, and for much helpful criticism. I am also greatly indebted to Dr. J. O. Irwin of the London School of Tropical Medicine for valuable advice on the statistical treatment.

*Note.* While this paper was in the press I have been privileged to have the criticism of Dr. Goodhart on two important points which require some explanation.

The first concerned the validity of excluding cases of organic pyloric stenosis. There were thirteen of these, and it will be seen from the criterion

which was used (resting juice of more than 150 c.c. and containing charcoal) that they do not correspond in any way to the 'pylorospasm' which is said to be associated with the climbing curve. Actually only one was classified as climbing, two as high plateau, and three as peak, so that the inclusion of these cases would evidently not tell in favour of duodenal regurgitation.

The second criticism was that the estimation of chlorides is essential to the interpretation of test-meal curves. It still appears to me that a fall in acidity can only be produced either by dilution or by neutralization, and however interesting it may be to watch the rise of neutral chlorides which occurs during these processes, no further information is obtained as to the source of the alkali. Exactly the same curves would be produced whether this comes from the stomach or from the duodenum, and the only hope of differentiating between these two possibilities lies in the use of some specific indicator of regurgitation such as bile.

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TABLE I

Classification.	No. of cases.	Average highest free acidity.	Average volume resting juice.	Average emptying time.	Average volume of residue.	% of specimens containing bile.	% of cases containing bile.	% of specimens containing mucus.	% of cases containing mucus.
1. Anacidity	74	0	27.9	1.622 ± 0.049	12.9 ± 4.1	16.0 ± 1.7	29.7 ± 5.3	59.4 ± 2.2	81.1 ± 4.6
2. Late secretion	13	15.2	34.7	1.885 ± 0.059	38.2 ± 15.6	17.3 ± 3.8	38.5 ± 13.5	51.0 ± 5.0	76.8 ± 11.7
3. Rising	58	31.0	38.0	1.737 ± 0.046	41.6 ± 9.0	12.7 ± 1.7	27.6 ± 5.9	29.0 ± 2.3	50.0 ± 6.6
4. Low plateau	76	26.4	40.0	1.895 ± 0.030	29.4 ± 5.1	13.3 ± 1.4	34.2 ± 5.5	44.5 ± 2.1	63.2 ± 5.5
5. High plateau	21	56.1	58.9	1.940 ± 0.035	21.3 ± 5.2	13.5 ± 2.7	42.9 ± 7.4	32.5 ± 3.7	52.4 ± 10.9
6. Climbing	45	66.1	38.3	1.850 ± 0.052	22.2 ± 7.1	11.7 ± 1.8	31.1 ± 6.9	33.0 ± 2.6	53.3 ± 7.4
7. Peak	102	35.8	43.5	1.880 ± 0.024	20.8 ± 3.5	15.0 ± 1.3	44.1 ± 4.9	47.3 ± 1.8	61.7 ± 4.8
7a. Fall corresponds	19	35.4	49.5	1.921 ± 0.078	29.0 ± 10.3	47.3 ± 4.1	100	41.1 ± 4.1	47.4 ± 11.4
7b. Fall does not correspond	83	35.9	42.2	1.870 ± 0.031	18.9 ± 3.3	7.44 ± 1.05	31.3 ± 5.1	48.7 ± 2.0	65.1 ± 5.2
8. Bile in more than two specimens	61	28.3	40.6	1.885 ± 0.038	26.6	62.2	100	44.1	62.3
Whole series	389	30.3	38.9	1.812 ± 0.017	24.8 ± 6.2	14.1 ± 0.66	35.2 ± 2.4	43.7 ± 0.9	62.7 ± 2.5
9. Not classified	65								
Total	454								

Note.—All the errors are standard errors; the probable error has not been used in any part of this paper.

TABLE II

*Comparison of Emptying Times.*

	Climbing curves.	Rising curves.
No. of cases	45 ( $n_1 + 1$ )	58 ( $n_2 + 1$ )
Mean ( $\bar{x}$ )	1.850 hrs.	1.737 hrs.
$S(x - \bar{x})^2$ . Sum of squares	5.351	6.960
Estimate of variance	$\frac{5.351}{44} = 0.1218$	$\frac{6.960}{57} = 0.1222$
Sampling variance of mean	$\frac{0.1218}{45} = 0.00271$	$\frac{0.1222}{58} = 0.00211$
Standard error of mean	$\pm \sqrt{0.00271} = \pm 0.052$	$\pm \sqrt{0.00211} = \pm 0.046$

Difference = 0.113 hrs.

Variance of difference =  $0.00271 + 0.00211 = 0.00482$ .

Standard error of difference =  $\pm \sqrt{0.00482} = \pm 0.069$  which is  $> \frac{0.113}{2}$ .

The difference is therefore not significant.

*Method of t.*

$$S^2 \left( \frac{1}{n_1 + 1} + \frac{1}{n_2 + 1} \right) = \frac{(5.351 + 6.960) \times 103}{45 \times 58 \times 101} = 0.00481.$$

$$t = \frac{0.113}{\sqrt{0.00481}} = 1.63 \quad n = 101.$$

From the table the probability that this value of  $t$  will be exceeded is between 0.1 and 0.2 so that the above result is confirmed.

TABLE III

*Percentage of Bile in Specimens.*

	No. of specimens.	No. containing bile.	% containing bile.
Peak curves	766	115	15.02
Climbing curves	333	39	11.72
Totals	1099	154	14.02

*Method I*

$$\text{Standard error of 15.02 is } \pm \sqrt{\frac{15.02 \times 84.98}{766}} = \pm \sqrt{1.67} = \pm 1.29.$$

$$\text{Standard error of 11.72 is } \pm \sqrt{\frac{11.72 \times 88.28}{333}} = \pm \sqrt{3.11} = \pm 1.76.$$

Difference = 3.30.

Standard error of difference =  $\pm \sqrt{1.67 + 3.11} = \pm 2.19$ .

The difference is therefore not significant.

*Method II*

Standard error of difference 3.30 is  $\pm \sqrt{14.02 \times 85.98 \left( \frac{1}{766} + \frac{1}{333} \right)} = \pm 2.28$   
which agrees well with the result given above.

TABLE IV

Type of curve.	Bile in more than two specimens.		Bile absent.	
	No. of cases.	% of cases.	No. of cases.	% of cases.
Anacidity	11	18.0	53	20.9
Late secretion	2	3.3	8	3.1
Rising	8	13.1	42	16.5
Low plateau	11	18.0	50	19.7
High plateau	3	4.9	12	4.7
Climbing	7	11.5	32	12.6
Peak	19	31.2	57	22.5
Totals	61	100.0	254	100.0

Note that the largest difference—31.2—22.5 = 8.7—is not significant, for its standard error is  $\pm 6.10$  (calculation as in Table III). These 61 curves contained 62.2 % of bile in specimens.

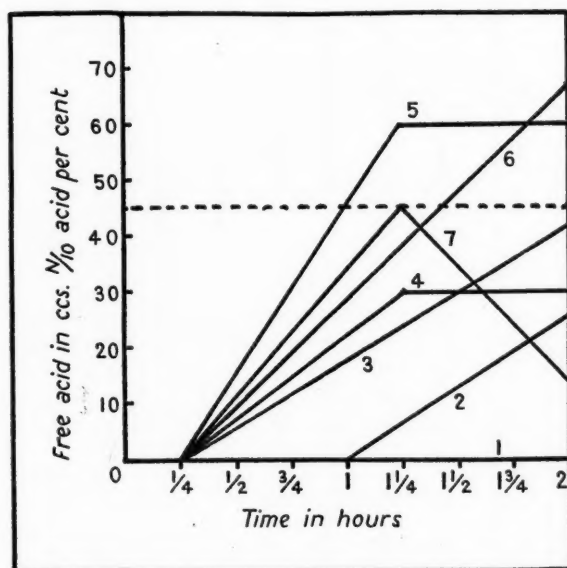


FIG. 1.

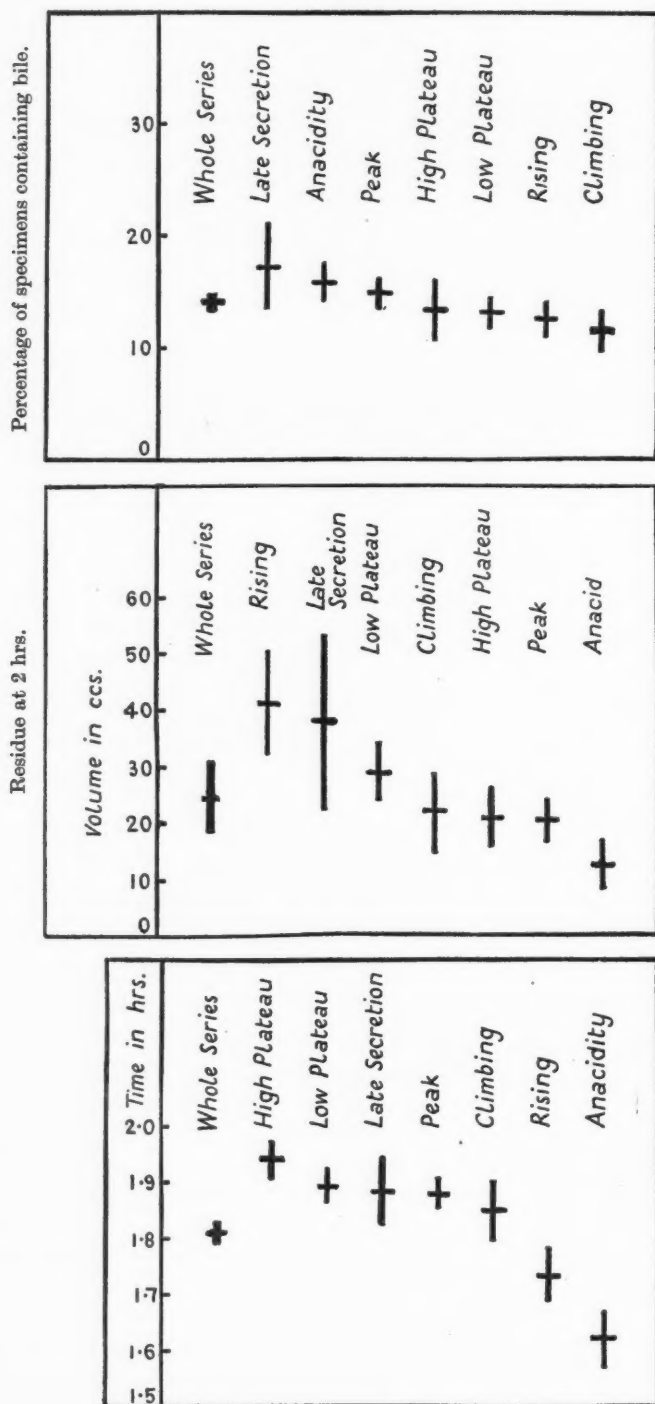


Fig. 4.

Fig. 3.

Fig. 2.

The vertical lines represent the means and the horizontal lines the standard errors.

Percentage of cases containing bile.

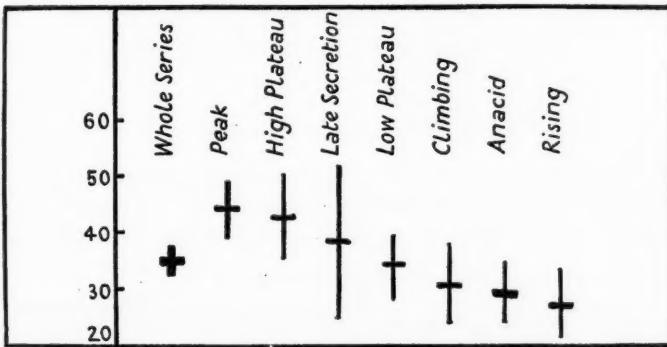


Fig. 5.

Percentage of specimens containing mucus.

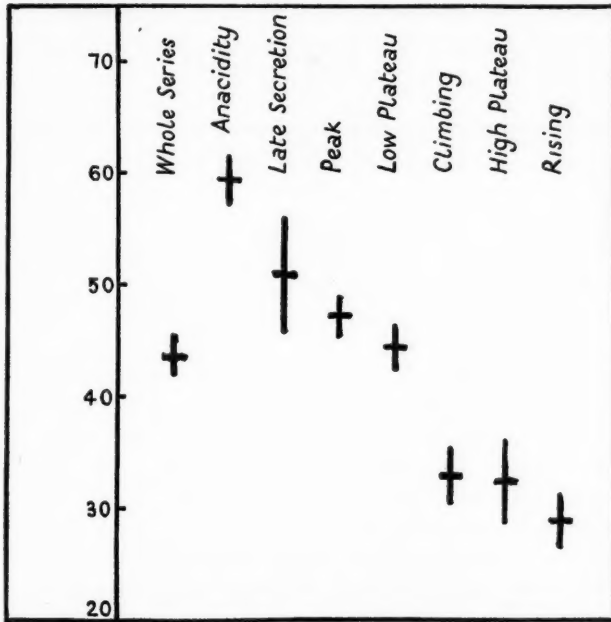


Fig. 6.

Percentage of cases containing mucus.

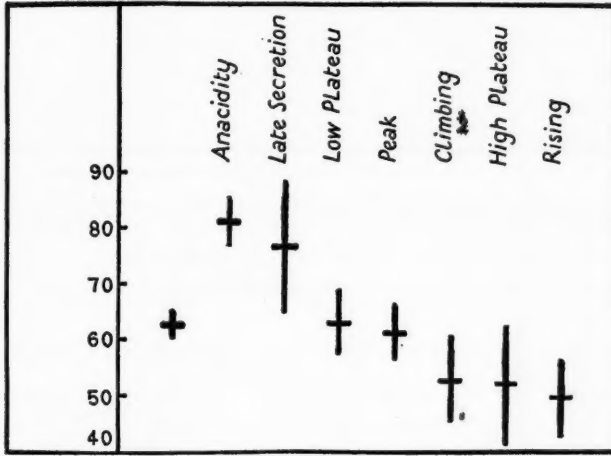
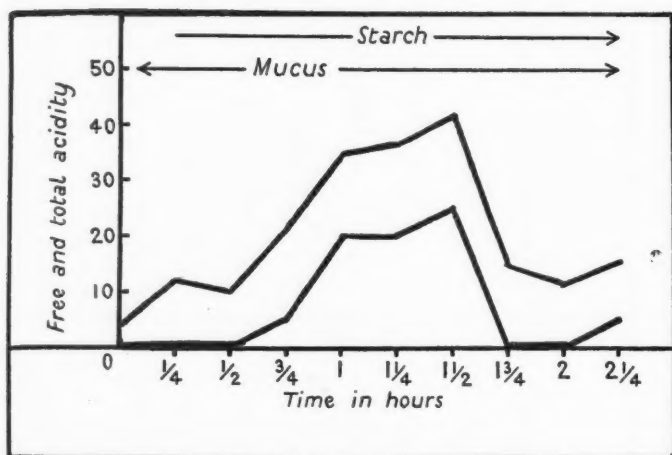


Fig. 7.

The vertical lines represent the means and the horizontal lines the standard errors.



Residue 105 c.c. Bile absent throughout.

FIG. 8.

## THE HAEMOPOIETIC ACTIVITY OF THE NORMAL AND ABNORMAL HUMAN LIVER

WITH SPECIAL REFERENCE TO PERNICIOUS ANAEMIA<sup>1</sup>

BY JOHN FREDERICK WILKINSON AND LOUIS KLEIN

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the University of Manchester)

IN previous communications (Wilkinson and Klein, 1932, 1933; Klein and Wilkinson, 1933) we described experiments which lent support to the theory that pernicious anaemia is a type of deficiency disease characterized by the absence from the gastric secretion of a specific enzyme that we named 'haemopoietin'. We found that when various fractions from hog's stomach containing the thermolabile enzyme haemopoietin were incubated with beef muscle, crude haemopoietically-active material was obtained which was relatively heat-resistant, and we considered that these experiments effected *in vitro* the synthesis of a substance allied to or identical with the active principle in liver. We suggested that the enzyme haemopoietin, by acting on a substrate present in a normal diet, might produce *in vivo* a substance which is stored as the active principle in liver until it is required for red-cell formation. Now, although the livers from various animals and fishes have been found to contain an active principle effective in the treatment of pernicious anaemia, the presence of a haemopoietically-active substance in the human liver has not so far been satisfactorily demonstrated. Since the theories we have put forward pre-supposed the presence of such an active principle in the liver of the normal human subject, and its absence in untreated cases of pernicious anaemia, it seemed of fundamental importance to test the haemopoietic activity of various normal and abnormal human livers as suitable opportunities arose for the satisfactory elucidation of this aspect of the problem. The present paper reports the results we have obtained, using carefully chosen pathological and clinical material.

### *Preparation of Liver Fractions*

IN view of the difficulties associated with the preparation of potent products for parenteral administration, we have thought it desirable to use the simplest and most widely-known method of extraction, so that our work

<sup>1</sup> Received January 18, 1934.

should be easy of repetition and confirmation by other workers. The extracts to be described were all given by intramuscular injection rather than intravenously, since the more highly purified extracts necessary for the latter method lose much of their potencies in their preparation. We have, therefore, carried out essentially the method described in the British Pharmacopoeia (1932) for the preparation of 'Extractum Hepatis Siccum'. The fractions so obtained (referred to below) were extremely hygroscopic and were preserved in vacuum desiccators until required. For use the weighed quantity of the appropriate fraction was dissolved in the minimum amount of water, filtered through a sterile Seitz filter and administered intramuscularly. The method was checked throughout by the preparation of similar potent extracts from fresh calf liver. Preliminary tests indicated that none of these extracts possessed any marked vasodepressor activity, while no ill effects were observed at any time when administered.

#### *Liver Extracts*

Fractions (corresponding to the potent anti-anaemic fraction of calf-liver) were prepared from suitably chosen livers to which the following short details refer:

(a) *Fractions from normal livers.* *Fraction L.I. 2.* A male, aged 58 years, died following the perforation of a duodenal ulcer. The autopsy did not disclose anything abnormal in the abdominal organs. The liver was normal macroscopically and microscopically. The fresh tissue (1,500 grm.) gave 34 grm. of fraction L.I.2.

*Fraction L.I. 6.* A male, aged 70 years, died following a traumatic cerebral haemorrhage. The autopsy did not show any macroscopic abnormalities in the abdominal organs. There was no atheroma of the blood-vessels. The liver appeared normal macroscopically and microscopically. It weighed 950 grm. and gave 16.5 grm. of fraction L.I.6.

*Fraction L.I. 7.* A male, aged 68 years, died from coronary atheroma and cardiac infarct. Autopsy did not show any gross disease of the internal organs. The liver was apparently normal, and section showed distension of the veins suggestive of chronic venous congestion. There was some fatty degeneration and infiltration of the liver cells but no evidence of cirrhosis. The liver weighed 1,200 grm. and gave 10 grm. of fraction L.I.7.

(b) *Fractions from livers of treated cases of pernicious anaemia in active remission.* *Fraction L.I. 4.* A man, aged 70 years, had been diagnosed as suffering from pernicious anaemia on 4.5.29 (blood count R.B.C's. 624,000; W.B.C's. 6,000; Hb. 18 per cent.; C.I. 1.4); he improved (29.5.29: R.B.C's. 2,608,000; Hb. 41 per cent.; C.I. 0.9) and had had remissions under treatment with liver and relapses until 13.4.33, when he was admitted to hospital with a count of R.B.C's. 568,000; W.B.C's. 2,000; Hb. 17 per cent.; C.I. 1.5. He improved again slightly, but took a premature discharge from hospital

against advice, and discontinued treatment. He was readmitted to hospital, and when seen by one of us for the first time had a blood count of R.B.C's. 620,000; W.B.C's. 3,000; Hb. 14 per cent.; C.I. 1.3; polymorphonuclears 72.0 per cent.; lymphocytes 21.0 per cent.; large mononuclears 2.0 per cent.; eosinophils 3.0 per cent.; basophils 2.0 per cent.; aniso- and poikilocytosis very marked; platelets scanty; normoblasts, myelocytes, polychromasia, and punctate basophilia present. He was a typical case of pernicious anaemia with a lemon-yellow colour, and complained of severe anaemia, palpitation, dyspnoea on exertion, sore tongue, indigestion, and flatulence with constipation. There were signs of bronchitis in the chest. He was given 4 c.c. of a commercial intramuscular liver extract on each of three days, and showed a rapid response to treatment; there was a reticulocyte crisis of 47.8 per cent. on the seventh day, and on the twentieth day the count was R.B.C's. 2,200,000; W.B.C's. 5,600; Hb. 38 per cent.; C.I. 0.9. Unfortunately, a double broncho-pneumonia supervened on the twelfth day and proved fatal on the twenty-third day. With a further 4 c.c. of intramuscular liver, given after the fatal complication had commenced, the patient had received a total of 16 c.c. of this very potent parenteral preparation of liver, of which 10 c.c. has been found adequate in an uncomplicated case of pernicious anaemia to produce complete remission from levels of 500,000 R.B.C's. per c.mm.

At necropsy there was extensive broncho-pneumonia in both lungs; the bone-marrow of the femur and sternum showed a moderate erythroblastic reaction, but no gross abnormalities in the other organs. Microscopically the kidneys showed gross ischaemic atrophy and arteriosclerosis of the renal vessels.

The liver contained a few scattered areas of focal necrosis; there was some haemosiderin in clumps of large granules in the centres of the liver columns, but only near the portal tracts, the Kupffer cells being free from it. The liver weighed 1,100 gm. and yielded 30 gm. of fraction L.I. 4.

*Fraction L.I. 8.* A woman, aged 65 years, was admitted to a hospital suffering from severe anaemia, weakness, shortness of breath on exertion, palpitation, marked indigestion and flatulence, sore tongue, constipation, pain in the back and legs with some paraesthesiae.

Examination confirmed the diagnosis of pernicious anaemia, and the count on admission was R.B.C's. 950,000; W.B.C's. 1,000; Hb. 25 per cent.; C.I. 1.3; polymorphonuclears 30.0 per cent.; lymphocytes 68.0 per cent.; large mononuclears 1.0 per cent.; basophils 0.5 per cent.; eosinophils 0.5 per cent.; no platelets seen; very marked aniso- and poikilocytosis and polychromasia; normoblasts, punctate basophilia and Howell-Jolly bodies present.

She was given a total of 14 c.c. of intramuscular liver extract over a period of three days, and responded very rapidly with a reticulocyte peak of 48.5 per cent. on the sixth day. On the twelfth day the blood count was R.B.C's. 1,950,000; W.B.C's. 7,000; Hb. 41 per cent.; C.I. 1.08. No further

treatment was given until the twenty-sixth day, when she developed pneumonia and the *Bacillus coli* was found in the urine. She was, therefore, given a further injection of intramuscular liver extract, amounting in all to 22 c.c., but she died from a double pneumonia with purulent parotitis, submaxillary adenitis and coli bacilluria. The patient thus received a total of 36 c.c. of intramuscular liver extract—an amount of this particular preparation that would have been sufficient for three uncomplicated cases.

Necropsy confirmed the cause of death, while the pernicious anaemia had apparently remitted. The bone-marrow in femur and sternum was normal in appearance and did not show hyperplasia. The heart showed well-marked fatty degeneration.

The spleen was firm, weighed 70 grm., and appeared normal, but section showed collections of haemosiderin in the endothelial cells lining the sinusoids.

The liver was of normal appearance macroscopically, while microscopically there was some fatty infiltration of moderate degree in the periportal areas, with a slight amount of haemosiderin periportally in the liver cells. The weight was 900 grm. and yielded 8 grm. of fraction L.I. 8.

*Fraction L.I. 9.* A woman, aged 73 years, was admitted to a hospital with a diagnosis of cardiac weakness and senility. She complained of a severe anaemia, palpitation, dyspnoea, indigestion, flatulence, progressive pallor, and paraesthesiae in the legs and hands. She had been ailing for three years. There was auricular fibrillation, lemon-yellow colour, no enlargement of the spleen and liver and no marked glossitis. She was doubly incontinent and practically moribund.

The blood count was R.B.C's. 912,000; Hb. 28 per cent.; C.I. 1.5; W.B.C's. 6,000; polymorphonuclears 64.0 per cent.; lymphocytes 30.0 per cent.; large mononuclears 4.0 per cent.; eosinophils 2.0 per cent.; basophils nil; platelets scanty; megalocytes, normoblasts, megaloblasts, polychromasia present; aniso- and poikilocytosis very marked.

She was given 18 c.c. of liver extract intramuscularly over a period of four days, and a prompt rise in reticulocytes (22 per cent. on the third day) was initiated, but the patient died with cardiac muscle failure on the fourth day. Autopsy confirmed the diagnosis of pernicious anaemia and cardiac muscle failure.

The bone-marrow showed marked erythroblastic reaction, and there was also a gross accumulation of polymorphonuclear cells with excessively lobulated nuclei; some haemosiderin was present in the reticulo-endothelial cells.

The stomach showed a moderate degree of superficial gastritis. The spleen contained much black and yellow pigments, chiefly in the phagocytes and also in the smooth muscle of the trabeculae; there was haemosiderin in the sinusoidal endothelium.

The liver, microscopically, showed marked variation in size and shape of

the cell nuclei; the sinusoids contained many leucocytes and other cells; the liver cells contained lipofuscin but no fat or haemosiderin; the Kupffer cells contained much haemosiderin. The liver weighed 1,300 gm. and gave 31 gm. of fraction L.I. 9.

*Fraction L.I. 13.* A market porter (Case 398), aged 45 years, was admitted to hospital suffering from a very severe degree of pernicious anaemia. He complained of breathlessness on exertion, weakness, palpitation, loss of strength, indigestion, flatulence, occasional soreness of the tongue, and a rapidly increasing anaemia with onset of a lemon-yellow colour of the skin. He stated that he had had a similar attack eighteen months previously, and had recovered after suitable treatment with liver, which, for financial reasons, he had been unable to continue. Examination disclosed a very marked anaemia with yellow mucous membranes and skin. There was a superficial glossitis, and the teeth were fairly good. The heart-rate was very rapid, and an aortic diastolic murmur was associated with a gallop rhythm. Spleen and liver were not enlarged, but there was marked tenderness under the left subcostal margin. The nerve reflexes were normal.

Blood count: R.B.C's. 430,000; Hb. 12 per cent.; C.I. 1.5; polymorphonuclears 75.0 per cent.; lymphocytes 23.5 per cent.; large mononuclears 1.0 per cent.; eosinophils, 0.5 per cent.; basophils nil; platelets scanty; aniso- and poikilocytosis well marked; no nucleated red cells seen; polychromasia and punctate basophilia present.

The patient was given 23 gm. of normal liver fraction L.I. 2 (equivalent to 1,015 gm. fresh tissue) intramuscularly, and responded extremely well, giving a reticulocyte peak of 61.8 per cent. on the tenth day, while the red-cell count rapidly rose on the fourteenth day to R.B.C's. 2,000,000; Hb. 39 per cent.; C.I. 0.97; W.B.C's. 5,000. He continued very well after this for a few days, when he developed acute double pneumonia following the visit of a relative suffering from influenza, and died three days later, with a count of R.B.C's. 2,000,000; W.B.C's. 8,000; Hb. 48 per cent.; C.I. 1.14; polymorphonuclears 95.5 per cent.; lymphocytes 3.0 per cent.; large mononuclears 1.5 per cent.; basophils nil; eosinophils nil; aniso- and poikilocytosis marked; platelets scanty.

Necropsy showed extensive confluent broncho-pneumonia in both lungs with a virulent pneumococcal pleurisy, but no gross abnormalities of the other organs.

Microscopical section showed the following: bone-marrow, an erythroblastic reaction with much haemosiderin in the reticulo-endothelial cells. Kidneys, very early nephritis repens; no haemosiderin found. Spleen, chronic venous congestion; some haemosiderin in the reticulo-endothelial cells. Liver, chronic venous congestion of moderate degree; much haemosiderin in the liver cells, particularly periportal.

The liver weighed 2,500 gm. and yielded 56 gm. of fraction L.I. 13.

(c) *Fraction from liver of partially treated case of pernicious anaemia in relapse.* *Fraction L.I. 1.* A man, aged 49 years, was admitted to a hospital

in extremis, suffering from pernicious anaemia. He had had a similar attack three years previously, from which he apparently recovered after suitable therapy, which he had since discontinued. He complained of shortness of breath on exertion, lassitude, weakness, extreme progressive yellowness and anaemia, indigestion, and diarrhoea. His brother had died from the same disease.

Examination confirmed the diagnosis of pernicious anaemia, the patient being in a moribund condition.

The blood count was R.B.C's. 880,000; W.B.C's. 2,200; Hb. 20 per cent.; C.I. 1.12; polymorphonuclears 51.0 per cent.; lymphocytes 45.75 per cent.; large mononuclears 1.0 per cent.; eosinophils 1.5 per cent.; basophils 0.75 per cent.; platelets very scanty; aniso- and poikilocytosis very marked; 7 normoblasts per 300 W.B.C's.; polychromasia and punctate basophilia present.

Before death the patient had apparently received intramuscularly 35 c.c. of a commercial liver extract, the potency of which we have reason to believe was of a very low grade.

Necropsy showed death was due to pernicious anaemia and pulmonary oedema. There was marked anaemia of all organs. The bone-marrow showed abundant hyperplasia and mitosis. The heart was enlarged and dilated with marked fatty infiltration and degeneration; both lungs were oedematous; stomach showed catarrhal gastritis; spleen much enlarged, hyperplastic, and congested; 'free iron' was present. The liver was enlarged, very brown in colour, and contained much 'free iron' throughout. It weighed 1,800 gm. and gave 18 gm. of fraction L.I. 1.

(d) *Fraction from liver of untreated fatal case of pernicious anaemia. Fraction L.I. 3.* A woman, aged 78 years, suffering from pernicious anaemia, was admitted to a hospital in a moribund comatose state. No history was obtained, and no treatment had been given prior to admission. Examination showed a wasted, edentulous woman, having markedly yellow skin and mucous membranes. The liver and spleen were not enlarged. Nerve reflexes were present. She died before any investigations or treatment could be carried out, but the blood count showed R.B.C's. 904,000; W.B.C's. 2,500; Hb. 29 per cent.; C.I. 1.6; polymorphonuclears 27.0 per cent.; lymphocytes 65.0 per cent.; large mononuclears 3.0 per cent.; eosinophils 5.0 per cent.; basophils nil; aniso- and poikilocytosis very marked; platelets very scanty; normoblasts, megaloblasts, and punctate basophilia present.

Necropsy confirmed the diagnosis of pernicious anaemia with chronic nephritis.

Microscopically there was much 'free iron' in the spleen, liver, and kidneys. The bone-marrow showed hyperplasia, and the liver exhibited fatty degeneration, much lipofuscin centrally, and large amounts of haemosiderin throughout the lobule, particularly in the liver cells.

The liver weighed 800 gm., giving 12.8 gm. of fraction L.I. 3

(e) *Fraction from liver of case of polycythaemia rubra. Fraction L.I. 14.*

A woman, aged 60 years, was admitted to hospital on 7.11.33, suffering from polycythaemia rubra with a blood count of R.B.C's. 9,020,000; W.B.C's. 27,500; Hb. 145 per cent.; C.I. 0.81; polymorphonuclears 84.75 per cent.; lymphocytes 11.50 per cent.; large mononuclears 2.25 per cent.; eosinophils 1.50 per cent.; basophils nil; aniso- and poikilocytosis very slight; platelets abundant; some punctate basophilia present. She died ten days later following a cerebral haemorrhage.

TABLE I

Liver fraction.	Clinical source of liver.		Test case no.
	Subject.	Cause of death.	
L.I. 1	Partially treated pernicious anaemia	Pernicious anaemia	350
L.I. 2	Normal human	Perforated duodenal ulcer	398
L.I. 3	Untreated pernicious anaemia	Pernicious anaemia	385
L.I. 4	Treated pernicious anaemia in remission	Broncho-pneumonia	388
L.I. 6	Normal human	Traumatic cerebral haemorrhage	384
L.I. 7	Normal human	Coronary atheroma, cardiac infarct	392
L.I. 8	Treated pernicious anaemia in remission	Broncho-pneumonia	393
L.I. 9	Treated pernicious anaemia in remission	Cardiac muscle failure	399
L.I. 10	Normal calf	—	396
L.I. 13	Treated pernicious anaemia in remission	Broncho-pneumonia	393
L.I. 14	Polycythaemia rubra	Cerebral haemorrhage	{ 296 400

Autopsy confirmed the diagnosis, there being extensive haemorrhages in the right cerebral hemisphere with considerable haemorrhages throughout the pia-arachnoid over the left hemisphere. There were some small ulcers in the pyloric region of the stomach. The spleen was enlarged and firm but normal in appearance. The bone-marrow showed marked erythroblastic reaction with very large numbers of megakaryocytes, while the cortex of the femur was very much thinned. In the tibia there were very small islets of haemopoietic tissue.

The liver was also very congested and showed great variation in the size of its cells and nuclei. It weighed 1,400 gm. and gave 32 gm. of fraction L.I. 14.

(f) *Fraction from calf's liver. Fraction L.I. 10.* For purposes of controlling the method of preparing the fractions, the corresponding fraction from calf's liver was prepared by exactly the same method as that used for the preparation of the human liver fractions. Thus 1 kg. of calf's liver yielded 29 gm. of fraction L.I. 10.

*The Clinical Response to the Experimental Liver Fractions.*

*Technique for testing haemopoietic activity.* The appropriate test fractions, prepared according to the method described above, were dissolved in the minimum amount of water, sterilized by filtration through a Seitz filter and administered intramuscularly in gradually increasing doses over a period of several days to suitably chosen and adequately controlled cases of pernicious anaemia; the effect on the reticulocyte count and on the red-blood cell count and haemoglobin percentage was noted. All the cases used in these experiments for testing the haemopoietic activity of the various liver fractions were carefully chosen so as to conform to the following criteria (Wilkinson, 1932, 1933): 1. The diagnosis of pernicious anaemia confirmed at least by a full blood count and the presence of achylia gastrica. 2. The absence of complications owing to their inhibiting effects. 3. An initial red-blood cell count not exceeding 1,750,000 per cubic millimetre. 4. No anti-anaemic treatment appeared to have been administered at a sufficiently recent date prior to the test so as to compromise it. 5. The patient was in hospital with careful control of diet and omission of any other additional treatment apart from the product under test. 6. A satisfactory control period of at least seven days at the beginning of the test, during which period it is essential that there should be no increase in the red-cell count, haemoglobin percentage and reticulocyte value in order to rule out the possibility of a spontaneous remission. 7. Response at the end of the control period. After the test product was administered the following changes were taken as a positive result indicating haemopoietic activity of the test product: (a) a steady and progressive reticulocyte response to a maximum within less than twelve days according to the dosage employed, and (b) a steady and progressive increase in the red-cell count and haemoglobin percentage following the exhibition of a reticulocyte crisis. 8. Progressive clinical improvement under the test treatment. 9. A reticulocyte crisis without an increase in the red-cell count and haemoglobin percentage or an increase in these two latter values without a reticulocyte crisis were not taken as definite results. If the patient failed to respond to the test product under the above conditions he was then given a known active preparation and a normal response was then obtained, as in paragraph seven, if the patient was a suitable one for the test.

In the following report of the test results we have omitted from the text repetition of figures for the preliminary control periods (as described above in paragraph 6) but we would emphasize that these were carried out in every case without exception and varied from seven to twenty-one days according to the patient. Only abbreviated clinical notes are given of illustrative cases.

(a) *Normal liver fractions (L.I. 2, 6, and 7). Case 384.* A housewife, aged 39 years, was admitted to hospital complaining of increasing weakness, palpitation, helplessness, and an aching pain in the right side of the

abdomen of varying intensity commencing February, 1933. Since July she had complained of severe progressive anaemia, with occasional vomiting, indigestion, flatulence, and loss of weight (2 stones in the previous twelve months). There was nothing relevant in the family and previous medical histories. Examination showed a severe degree of anaemia, pallor of mucous membranes, and superficial glossitis. The spleen was tender and just palpable below the left subcostal margin. There was nothing abnormal in the nervous system. Fractional gastric analysis showed achylia gastrica; the Wassermann reaction was negative. Radiographic examinations: *Colon*—'the enema flowed freely to the caecum; the outline of the transverse and descending colon was rather irregular suggesting diverticulitis, though no individual diverticula were seen; there was no evidence of carcinoma of the caecum'. *Chest*—'there was an area of consolidation just below the centre of the left clavicle with a little fibrosis leading from this area to the left hilar region. The appearances suggested localized tuberculous pneumonia, probably healed'.

Blood count: R.B.C's. 1,544,000; Hb. 45 per cent.; C.I. 1.50; W.B.C's. 3,600; polymorphonuclears 57.0 per cent.; lymphocytes 39.0 per cent.; large mononuclears 3.0 per cent.; eosinophils nil; basophils 1.0 per cent.; aniso- and poikilocytosis marked; platelets scanty; no abnormal staining.

After the preliminary control period without treatment the patient was given 11 grm. of liver fraction L.I. 2, and 13 grm. of fraction L.I. 6. (equivalent to 1,235 grm. fresh liver) during seven days. A very good response was obtained, the reticulocytes rising to a maximum of 42 per cent. on the eleventh day of treatment and there were also rapid rises in the red-cell count and haemoglobin percentage.

Day of treatment.	Reticulocytes.	Red-blood cells.	Haemoglobin.
4	2.0 per cent.	1,390,000	35 per cent.
11	42.0 " "	1,680,000	37 " "
25	1.4 " "	2,550,000	62 " "

*Case 392.* A housewife, aged 76 years, was admitted to hospital complaining of nausea and vomiting, loss of appetite and weight, increasing anaemia, weakness, shortness of breath, indigestion, and flatulence. In 1923 she had a cholecystitis and in 1932 she received radium treatment for an epithelioma of the mucous membrane of the left cheek, making a good recovery. Since then she had gradually gone downhill and pernicious anaemia had developed very rapidly during the four weeks prior to admission.

Examination showed a thin edentulous woman; the liver was palpable and there was some tenderness under the right subcostal margin; the spleen was not enlarged; systolic murmurs were present at the mitral and aortic areas; knee and ankle-jerk reflexes were not elicited and plantar responses were flexor.

Blood count: R.B.C's. 1,060,000; Hb. 30 per cent.; C.I. 1.50; W.B.C's. 4,600; polymorphonuclears 49.0 per cent.; lymphocytes 46.5 per cent.; large mononuclears 4.0 per cent.; eosinophils 0.5 per cent.; basophils nil; aniso- and poikilocytosis very marked; platelets scanty; punctate basophilia and polychromasia present. Fractional gastric analysis showed achylia gastrica. The Wassermann reaction was negative.

After the control period without treatment she received 10 grm. of liver fraction L.I. 7 (equivalent to 1,200 grm. normal liver) during four days. A good response was obtained, the reticulocytes rising to a maximum of

30.1 per cent. on the seventh day of treatment. There were also rapid increases in the red-cell counts and haemoglobin percentages.

Day of treatment.	Reticulocytes.	Red-blood cells.	Haemoglobin.
1	3.0 per cent.	1,120,000	31 per cent.
7	30.1 " "	1,580,000	38 " "
15	4.0 " "	2,460,000	54 " "
22	1.1 " "	2,940,000	63 " "

In addition to the two cases just described, a third patient (Case 398, reported on a previous page) was also treated with normal human liver (fraction L.I. 2) and responded well, showing a reticulocyte crisis of 61.8 per cent.

These three cases all illustrate the haemopoietic potency of extracts of human liver in the treatment of pernicious anaemia.

(b) *Liver fractions (L.I. 4, 8, 9, and 13) from treated cases of pernicious anaemia in remission.* Case 388. A salt worker, aged 65 years, was admitted to hospital complaining of shortness of breath, palpitation, nausea, and vomiting in the mornings and loss of energy: there was no history of sore tongue or diarrhoea.

Examination: an edentulous man with lemon-yellow skin; slightly icteric conjunctivae; tongue practically normal; some small, soft, discrete mobile glands in the neck. Nervous system normal. Spleen not enlarged, liver just palpable, no tenderness.

Fractional gastric analysis showed achylia gastrica. Wassermann reaction was negative.

Blood count: R.B.C's. 1,250,000; W.B.C's. 5,500; Hb. 32 per cent.; C.I. 1.28; polymorphonuclears 57.0 per cent.; lymphocytes 39.5 per cent.; large mononuclears 3.0 per cent.; eosinophils 0.5 per cent.; basophils nil; aniso- and poikilocytosis marked; platelets scanty; no abnormal staining; one normoblast per 200 white cells.

After the control period he received 30 grm. of liver fraction L.I. 4 (equivalent to 1,100 grm. liver) during eight days. A fairly good haematological response was obtained, although the reticulocytes only rose to a maximum of 16.8 per cent. on the eleventh day of treatment.

Day of treatment.	Reticulocytes.	Red-blood cells.	Haemoglobin.
1	2.2 per cent.	1,490,000	38 per cent.
11	16.8 " "	1,520,000	48 " "
16	3.4 " "	2,300,000	64 " "
23	0.9 " "	3,260,000	78 " "

Case 393. A housewife, aged 56 years, was admitted to hospital complaining of recurring attacks of nausea and vomiting during the previous nine months, weakness, shortness of breath, loss of weight, palpitation, some indigestion and flatulence, no sore tongue or diarrhoea. Examination showed a rather well-built woman with biscuit-coloured complexion; atrophic glossitis; marked anaemia and pallor of mucous membranes; nothing abnormal in the lungs, heart, or nervous system. There was some tenderness over the liver and spleen, but no definite enlargement. Fractional gastric analysis disclosed achylia gastrica, the Wassermann reaction was negative; while the blood count was R.B.C's. 1,280,000; W.B.C's. 1,700; Hb. 43 per cent.; C.I. 1.65; polymorphonuclears, 55.5 per cent.; lymphocytes, 41.5 per cent.; large mononuclears 2.5 per cent.; eosinophils 0.5 per cent.; basophils nil; aniso- and poikilocytosis marked; platelets scanty; some polychromasia and punctate basophilia; no nucleated red cells seen.

After the control period without treatment she received 8 grm. of liver fraction L.I. 8 (equivalent to 900 grm. liver) during three days. Only a fair response was obtained the reticulocytes rising to 8.7 per cent. and the blood count to 1,800,000 red cells and 46 per cent. haemoglobin on the sixth day. Thereafter the count slowly fell again in the course of the next sixteen days—(no treatment being given in that time)—to R.B.C's. 1,540,000; Hb. 47 per cent.; W.B.C's. 4,100; C.I. 1.7.

From the twenty-third to the thirty-first day she was given a total of 41 grm. of liver fraction L.I. 13 (equivalent to 1,830 grm. liver) with only a maximum reticulocytosis of 16.2 per cent. on the thirty-first day. The blood count rose to R.B.C's. 3,300,000; W.B.C's. 5,400; Hb. 73 per cent. C.I. 1.1 on the forty-third day.

Day of treatment.	Reticulocytes.	Red-blood cells.	Haemoglobin.
1	2.8 per cent.	1,280,000	43 per cent.
	8 grm. fraction L.I. 8 in 3 days.		
6	8.7 per cent.	1,800,000	46 " "
14	2.7 " "	1,650,000	49 " "
22	3.0 " "	1,540,000	47 " "
23	41 grm. fraction L.I. 13 in 9 days.		
31	16.2 per cent.	1,880,000	46 " "
36	3.8 " "	2,700,000	66 " "
43	0.8 " "	3,300,000	73 " "

*Case 399.* A housewife, aged 34 years, was admitted to hospital complaining of recurrent attacks of vomiting, loss of energy, shortness of breath, palpitation, paraesthesiae in the fingers and toes, loss of weight, soreness of the tongue, indigestion, and flatulence. Family history—a sister of the patient also suffering from pernicious anaemia was already under the care of one of us. Examination showed atrophic glossitis, some carious teeth, very pale mucous membranes; pupils both irregular; liver slightly enlarged, but not the spleen; systolic murmurs heard over the whole praecordium; pulsation in the veins of the neck; nothing abnormal in the lungs and nervous system; knee-jerks only obtained on reinforcement. Fractional gastric analysis—achylia gastrica. Wassermann reaction negative.

Blood count: R.B.C's. 580,000; W.B.C's. 4,600; Hb. 17 per cent.; C.I. 1.42; polymorphonuclears 58.0 per cent.; lymphocytes 36.5 per cent.; large mononuclears 3.5 per cent.; eosinophils 1.0 per cent.; basophils 1.0 per cent.; aniso- and poikilocytosis very marked; platelets very scanty; one normoblast per 100 white cells; polychromasia and punctate basophilia present.

She received 31 grm. of liver fraction L.I.9 (equivalent to 1,300 grm. liver) during six days after the preliminary control period. Good clinical and moderate haemopoietic responses were obtained. The reticulocyte crisis reached 34.8 per cent. on the seventh day and a second peak of 38.2 per cent. was obtained on the eleventh day—a slight fall to 24 per cent. occurring between them. The result was suggestive of insufficient dosage or submaximal potency of the fraction. The blood count showed a good response as shown in the table.

Day of treatment.	Reticulocytes.	Red-blood cells.	Haemoglobin.
1	2.7 per cent.	580,000	17 per cent.
7	34.8 " "	928,000	21 " "
11	38.2 " "	1,320,000	32 " "
14	2.8 " "	1,530,000	36 " "
21	2.4 " "	1,560,000	46 " "

These three cases seem to indicate that the liver content of the haemo-poietic principle is increased in patients with pernicious anaemia undergoing effective treatment. In none of these tested did the enhanced potencies equal those of the normal livers, but this may be due to the fact that the blood counts had not reached normal values.

It is extremely interesting to note that 1,015 gm. of normal liver tissue (as fraction L.I. 2) was sufficient to produce (a) an excellent clinical and haematological response in a severe case of pernicious anaemia (Case 398) who subsequently died as a result of an intercurrent pneumonia, and (b) fraction L.I. 13 (prepared from the liver of this patient (Case 398)) which was sufficiently potent for the treatment of Case 393.

That is to say, normal liver fraction L.I. 2 after passage through Case 398 was still sufficiently potent to initiate a remission in Case 393.

(c) *Effect of the liver fraction L.I. 1 derived from a partially treated relapsing case of pernicious anaemia. Case 350.* A labourer, aged 52 years, was admitted to hospital complaining of increasing weakness of the arms and legs during the last four years, shortness of breath, fatigue on slight exertion, soreness of the tongue, paraesthesiae in the fingers and toes, occasional diarrhoea, no loss of weight or appetite, some indigestion and flatulence and complete loss of sense of smell and taste for the previous two years.

Examination showed lemon-yellow colour, atrophic glossitis, very marked anaemia; heart, lungs, and abdomen did not show anything abnormal. The liver and spleen were not palpable.

Nerve reflexes were present and normal. The Wassermann reaction was negative. Fractional gastric analysis showed achylia. Blood count: R.B.C's. 1,750,000; W.B.C's. 3,200; Hb. 48 per cent., C.I. 1.2; polymorphonuclears 27.25 per cent.; lymphocytes 47.25 per cent.; large mononuclears 3.5 per cent.; eosinophils 21.75 per cent.; basophils 0.25 per cent.; aniso- and poikilocytosis well marked; platelets scanty; nucleated red cells present and occasional Türk cells.

He was given 6.0 gm. of liver fraction L.I. 1 (equivalent to 600 gm. liver) and the maximum reticulocyte response of 10.7 per cent. occurred on the eighth day with only a moderate increase in the red-cell count and haemoglobin percentage on the fifteenth day to 1,780,000 and 52 per cent. respectively.

There was a good response subsequently following parenteral treatment with liver extract ('Hepastab').

(d) *Effect of liver fraction (L.I. 3) from an untreated fatal case of pernicious anaemia. Case 385.* A grocer, aged 56 years, was admitted to hospital complaining of weakness, loss of weight and energy, palpitation, shortness of breath, and attacks of severe vomiting at irregular intervals during six months prior to admission. There was no history of haematemesis, but he had had indigestion and flatulence without sore tongue or diarrhoea. Examination showed an edentulous, pale yellow, thin, small man who had been completely bald since childhood. There was no enlargement of the spleen or liver, and nothing abnormal to be found in the lungs, abdomen, or nervous system. The Wassermann reaction was negative. Fractional gastric analysis showed achylia gastrica. Blood count: R.B.C's. 1,340,000; W.B.C's. 1,200; Hb. 28 per cent.; C.I. 1.08; polymorphonuclears 63.0 per cent.; lymphocytes 30.0 per cent.; large mononuclears 2.0 per cent.;

eosinophils 5.0 per cent.; basophils nil; aniso- and poikilocytosis very marked; platelets scanty; one normoblast per 100 white-blood cells.

After the preliminary control period he was given 11 gm. of liver fraction L.I. 3 (equivalent to 690 grm. liver) during a period of four days. There was no haematological response, indicating the absence of potency in this liver fraction, while the red-cell count and haemoglobin fell very rapidly with a severe relapse clinically. The patient, however, responded normally after the administration of a known active liver preparation (see table).

Day of treatment.	Reticulocytes.	Red-blood cells.	Haemoglobin.
Control { -15	4.0 per cent.	1,340,000	28 per cent.
period { -2	3.0 " "	1,230,000	30 " "
1	11 gm. fraction L.I. 3 given over 4 days		
6	2.4 per cent.	990,000	22 " "
9	1.8 " "	980,000	17 " "
10	24 c.c. potent intramuscular liver extract over 5 days		
15	38.0 per cent.	940,000	25 per cent.
17	22.8 " "	1,230,000	30 " "
21	15.8 " "	1,640,000	35 " "
28	4.1 " "	2,660,000	51 " "
35	0.8 " "	3,000,000	63 " "

(e) *Effect of liver fraction (L.I. 14) from case of polycythaemia rubra. Case 296.* A housewife, aged 47 years, was admitted to hospital complaining of severe progressive anaemia, weakness, lack of energy, shortness of breath, nausea, vomiting, indigestion, flatulence, paraesthesiae in the legs, sore tongue and marked yellowness of the skin.

Examination showed severe anaemia, lemon-yellow colour, atrophic glossitis, enlarged liver and spleen and an absence of the knee-jerk reflex on the left side.

Blood count on admission was: R.B.C's 1,340,000; W.B.C's. 3,000; Hb. 30 per cent.; C.I. 1.16. The fractional gastric analysis showed achylia gastrica; Wassermann reaction was negative.

After a preliminary control period of twenty-two days the blood count was R.B.C's. 1,140,000; W.B.C's. 2,400; Hb. 31 per cent.; C.I. 1.17; polymorphonuclears, 58.5 per cent.; lymphocytes 36.5 per cent.; large mononuclears 2.0 per cent.; eosinophils 3.0 per cent.; basophils nil; platelets scanty; aniso- and poikilocytosis very marked; polychromasia and punctate basophilia present; normoblasts 1.5 per cent. of white cells.

She was given 15 gm. of liver fraction L.I. 14 and there was a very prompt haematological response, a maximum of 41.6 per cent. reticulocytes being reached on the sixth day.

Day of treatment.	Reticulocytes.	Red-blood cells.	Haemoglobin.
1	3.0 per cent.	1,140,000	31 per cent.
6	41.6 " "	—	—
8	19.0 " "	1,740,000	33 per cent.
15	6.8 " "	3,010,000	55 " "

*Case 400.* An electrical worker, aged 44 years, was admitted to hospital complaining of recurrent attacks of nausea, vomiting, and diarrhoea together with progressive weakness and tiredness, being ultimately unable to follow his normal employment.

He complained of soreness of the tongue, shortness of breath, swelling of the legs and feet, indigestion, slight flatulence, loss of weight, but there were no symptoms affecting the nervous system. The bowels were regular and

normal. There was a history of malaria and gastritis eighteen years previously, but nothing relevant in the family history.

Examination showed marked anaemia, yellow skin, atrophic glossitis; the liver and spleen were not enlarged, but there was some tenderness in the epigastrium; nervous reflexes were normal; there was a mitral systolic murmur of haemic origin. There was achylia gastrica. The Wassermann reaction was negative.

On admission the blood count was as follows: R.B.C's. 1,480,000; W.B.C's. 6,000; Hb. 34 per cent.; C.I. 1.13; polymorphonuclears 55.5 per cent.; lymphocytes 37.0 per cent.; large mononuclears 4.0 per cent.; eosinophils 2.5 per cent.; basophils 1.0 per cent.; aniso- and poikilocytosis very marked; platelets scanty; megalocytes, polychromasia and punctate basophilia present; normoblasts 2.0 per cent. of white cells.

He was the subject of a series of negative investigations from this time onward giving a subsequent control period of several weeks. At the end of this time the blood count was: R.B.C's. 1,390,000; W.B.C's. 6,800; Hb. 33 per cent.; C.I. 1.2; and the reticulocyte counts had not risen above the normal values.

He was given 10 grm. of liver fraction L.I. 14 intramuscularly and showed a very satisfactory response (see table), the maximum reticulocyte response being 30.1 per cent. on the sixth day of treatment. There was an extremely rapid rise in the red-cell count and haemoglobin percentage in the subsequent fortnight.

Day of treatment.	Reticulocytes.	Red-cell count.	Haemoglobin.
1	3.2 per cent.	1,390,000	33 per cent.
6	30.1 " "	—	—
8	9.4 " "	2,630,000	44 " "
14	1.2 " "	3,090,000	50 " "

(f) *Control case. Effect of fraction (L.I. 10) from calf's liver. Case 396.* A man, aged 52 years, was admitted to hospital complaining of feeling run down since an attack of influenza some months previously. His main symptoms were shortness of breath and energy, indigestion and flatulence, with nausea and vomiting, paraesthesiae in the feet, frequent headaches, and occasional tinnitus. He had continually been 'off colour' for the last few years.

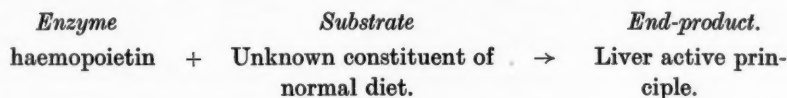
Examination: Lemon-yellow skin, conjunctivae obviously anaemic, smooth tongue, pulse rapid and regular, heart-sounds normal. Nothing abnormal in the lungs; some general tenderness over abdomen; liver not enlarged; spleen just palpable. Nervous system normal. The Wassermann reaction was negative. Fractional gastric analysis disclosed achylia gastrica. Blood count: R.B.C's. 930,000; W.B.C's. 2,000; Hb. 26 per cent.; C.I. 1.36; polymorphonuclears 45.5 per cent.; lymphocytes 52.0 per cent.; large mononuclears 2.5 per cent.; eosinophils nil; basophils nil; platelets scanty; marked aniso- and poikilocytosis with punctate basophilia and polychromasia; normoblasts 1.0 per cent. of white cells.

He was given 29 grm. of liver fraction L.I.10 (equivalent to 1,000 grm. calves' liver) during six days after the preliminary control period. There was a very good response, the reticulocytes rising to 54.7 per cent. on the ninth day of treatment.

Day of treatment.	Reticulocytes.	Red-blood cells.	Haemoglobin.
1	1.6 per cent.	760,000	19 per cent.
9	54.7 " "	1,130,000	31 " "
15	14.8 " "	1,470,000	40 " "

*Discussion*

We have long held the opinion that one of the many functions of the liver is that of storing the so-called anti-anaemic principle of liver and making it available as and when required by the haemopoietic system. The presence of this 'liver principle' in the normal human liver is, of course, to be anticipated since it has been found to be present in the livers of a large number of animals and fishes. On the other hand, its absence from the livers of patients dying from pernicious anaemia would be in harmony with the hypothesis that the liver principle is formed in the normal individual by the action of the enzyme haemopoietin on some substance present in the normal diet according to the following:



It is therefore suggested that this reaction can no longer take place in these patients with pernicious anaemia, since they have achylia gastrica, and there is an almost complete absence of any known enzyme secretion into their stomachs (Wilkinson, 1932).

We have found the modern treatment of pernicious anaemia so efficient that we have experienced considerable difficulty in obtaining post-mortem material from our own series of cases to enable us to test these views by direct experiment in an adequately controlled and satisfactory manner. Through the co-operation of others, however, we have been fortunate enough to get suitable specimens from other external sources, and we believe that we have now obtained sufficient results to enable us to draw certain conclusions. Similar attempts were made by Richter, Ivy, and Kim (1932) using extracts from two cases, but their experiments are not convincing since they were quite uncontrolled, while their test cases and clinical responses obtained are open to question both qualitatively and quantitatively and do not conform to the criteria that we consider necessary for such test experiments (cp. page 348).

In our own observations we used ten separate liver fractions prepared by the same method from human livers obtained during the last four years. For comparative purposes the results obtained with one calf-liver fraction are also included. These observations are, we believe, sufficiently clear cut and free from doubt to enable us to make reasonable deductions from them.

When the first human liver fractions were prepared, we were not so familiar with a satisfactory method of preparing highly potent liver preparations for intravenous use (compare Wilkinson 1931) and the doses employed were somewhat high; further, the crude human tissue has only become available from time to time and in varying weight. As we wished

to make a direct comparison of all the fractions, we have, therefore, been careful to use the same process throughout, and where possible roughly the same amount of moist fresh tissue.

On the basis of our experimental results the livers of which the haemopoietic activities were tested, fall automatically into the following groups according to the activity of the fraction obtained from them:

Group I. *Haemopoietically active livers.* (a) Normal human livers.  
(b) Livers of treated cases of pernicious anaemia in active remission.  
(c) Livers from cases of polycythaemia rubra.

Group II. *Livers with reduced haemopoietic potency.* Livers from partially or inadequately treated pernicious anaemia in relapse or the early stages of remission.

Group III. *Haemopoietically inactive livers.* Livers from untreated fatal cases of pernicious anaemia.

A comparison of the approximate haemopoietic potencies of the various fractions used by us is shown in Table II.

Referring to this table, it will be seen very clearly that the calf and normal human liver fractions are of approximately equal potency as regards their content of the anti-anaemic principle, while the liver fraction from the case of polycythaemia rubra was definitely more potent, yielding better and more rapid remissions.

Liver fractions obtained from cases of pernicious anaemia in remission, but dying from other causes, showed less degrees of potency suggesting that the livers had much smaller contents of the anti-anaemic principle. This was to be expected since in each 'donor' case, the blood picture had not had time to return to normal before the fatal termination. Only one opportunity presented itself for investigating the liver fraction from a partially treated case of pernicious anaemia, and this was due to the use of a commercial liver preparation that had only slight haemopoietic potency and the patient probably received only a very small amount of the active liver principle. The liver fraction (L.I. 1) from this case contained negligible quantities of the anti-anaemic principle when tested clinically.

The fraction from an untreated case of pernicious anaemia was haemopoietically inactive.

Thus it is clear that the haemopoietic potencies of livers from apparently normal men and from cases of pernicious anaemia in remission as well as polycythaemia rubra are at least equal to those of animal and fish livers.

On the other hand, in untreated fatal pernicious anaemia, we have shown by clinical experiment that the liver is apparently devoid of any haemopoietic activity. This is in harmony with the view we have previously put forward (Wilkinson and Klein, 1933) that pernicious anaemia is a deficiency disease characterized in the first place by the absence of a specific enzyme, haemopoietin, from the gastric secretion, as a result of which there is a failure to produce the anti-anaemic principle (or possibly

a precursor) for absorption. There is also a possibility that in certain similar cases of megalocytic (non-Addisonian) anaemias (e.g. associated with idiopathic steatorrhoea, sprue, &c.), lack of absorption may play a not inconsiderable part (Bennett, Hunter, and Vaughan, 1932).

A logical conclusion would thus be that pernicious anaemia develops, or a relapse occurs, in those cases in which the liver is depleted of its store of the so-called 'anti-anaemic principle'.

It is now well established that effective treatment of such cases of pernicious anaemia involves at present the use of preparations of animal livers or pig's stomach. In the former case, the missing anti-anaemic factor is directly placed at the disposal of the haemopoietic system; whilst in the latter case it is formed by the action of the enzyme haemopoietin present in the pig's stomach on an unknown substrate found in a normal diet and also present in dead stomach tissue. The deficient anti-anaemic factor is thus supplied from external sources, and any excess is then stored in the liver.

In this connexion, however, it is interesting to note that one fraction (L.I. 2) prepared from a normal human liver not only produced a good remission in one patient (Case 398), but was able by passage through the liver of that patient to yield a potent liver fraction (L.I. 13) for the treatment of a further patient (Case 393), notwithstanding the fact that much of the active principle is probably lost during the preparation of these fractions. There would appear, therefore, to be at least three possibilities. In the first place, passage through the first patient (Case 398) may have enhanced the potency of the original fraction (L.I. 2); secondly, a very large excess of the fraction (L.I. 2) may have been given originally to the first patient (Case 398), although this is unlikely in view of the haematological and clinical responses; or, finally, the remission having been initiated by the potent fraction (L.I. 2), some other factor or factors may have come into play enabling the haemopoietic system to carry on, and even store up, the liver principle or similar substance without further immediate supplies of the liver principle itself from external sources.

It is an interesting speculation in this clinical experiment as to the source of the anti-anaemic principle present in the liver fraction L.I. 13 obtained from the liver of the first test patient (Case 398). It may represent part of the total amount originally present in the normal human liver fraction L.I. 2 that was administered to that patient; this view receives some support from the success claimed by the 'depot' method of treating pernicious anaemia with parenteral liver extracts. On the other hand, it may have been formed by some other, as yet unknown, process taking place (in Case 398) following the initiation of the remission; this appears to be less likely and would suggest hitherto unsuspected mechanisms.

TABLE II  
*Comparison of Responses to Various Liver Extracts Intramuscularly*

Source of liver.	Test case no.	Liver fraction.	Dose of liver in grammes of fresh tissue.	Reticulocytes.		Initial count.		Count at end of 15 $\pm$ 1 days.	
				Max. %.	Day of treatment.	R.B.C. $\times 10^6$ .	Hb. %.	R.B.C. $\times 10^6$ .	Hb. %.
Calf	396	L.I. 10	1,000	54.7	9	0.760	19	1,470	40
Normal human	384	L.I. 2 + L.I. 6	1,235	42.0	11	1.390	35	2,600	53
	392	L.I. 7	1,200	30.1	7	1.120	31	2,460	54
	398	L.I. 2	1,015	61.8	10	0.430	12	2,000	39
	388	L.I. 4	1,100	16.8	11	1.490	38	2,300	64
Remitting pernicious anaemia	393	L.I. 8	900	8.7	6	1.280	43	1,650	49
	393	L.I. 13	1,830	16.2	8	1.540	47	2,700	66
	399	L.I. 9	1,300	34.8	7	0.580	17	1,530	36
Partially treated pernicious anaemia	350	L.I. 1	600	10.7	8	1.750	48	1,780	52
	385	L.I. 3	690	No response		1.230	30	0.940	25
Polycythaemia	296	L.I. 14	660	41.6	6	1.140	31	3,010	55
	400	L.I. 14	440	30.1	6	1.390	33	3,090	50

*Summary*

Extracts of ten livers from normal and abnormal human subjects have been examined for their haemopoietic potencies as judged by clinical trial on cases of pernicious anaemia. The results show definitely that the anti-anaemic 'liver principle' is present in normal human livers and in livers from treated cases of pernicious anaemia in active remission, but is absent from the livers of untreated cases of pernicious anaemia.

The liver from a case of polycythaemia rubra was found to be more potent than normal human or calf livers.

The bearing of these results on the aetiology of pernicious anaemia is discussed, and it is shown that they are in harmony with the hypothesis we have previously put forward that the liver acts as a storehouse for an anti-anaemic factor (the 'liver active principle') which is produced in the stomach as a result of enzyme action between haemopoietin (the 'stomach active principle') and an unknown constituent of a normal diet.

We are greatly indebted to those who have been able to supply us with the crude material necessary for this work, and to the Medical Research Council, London, for a grant which has enabled one of us (L.K.) to take part in it.

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THE ALLEGED PITUITARY ORIGIN OF THE ECLAMPTIC  
AND PRE-ECLAMPTIC 'TOXAEMIAS' OF PREGNANCY<sup>1</sup>

BY F. B. BYROM AND C. WILSON

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THE suggestion that the pre-eclamptic and eclamptic toxæmias of pregnancy arise from overactivity of the pituitary gland appears to have been first advanced by Hofbauer (5) in 1918. The idea has obvious attractions in that pituitrin, which is prepared from the posterior and intermediate lobes of the gland, and is probably secreted by the cells of the latter, possesses antidiuretic and pressor properties. Furthermore the activity of the gland is known to be altered during pregnancy.

In the last few years evidence in favour of the speculation has been presented from three independent sources. These are the observations of H. Küstner (6) on the effect of eclamptic serum on the melanophores of the frog's skin; those of H. Cushing (4) concerning invasion of the posterior lobe by basophilic cells from the pars intermedia in eclampsia and other hypertensive states; and the claim of K. J. Anselmino and F. Hoffmann (1) (2) to have obtained pressor and antidiuretic effects with ultrafiltrates of blood-plasma obtained from cases of pre-eclamptic and eclamptic toxæmias. Since there is no evidence that the pituitary controls pigmentation in man, evidence derived from the behaviour of frog melanophores can be regarded as only circumstantial. The writings of Cushing on basophilic hyperplasia are more direct and come from the pen of an acknowledged authority on the pathological physiology of the pituitary, but much more information is needed concerning the normal limits of basophilic invasion before mature conclusions will be permissible. There remains the evidence of Anselmino and Hoffmann, and the present paper is based on attempts to confirm their claim that toxæmic blood contains demonstrable amounts of an antidiuretic substance. The more difficult problem of demonstrating pressor activity has not been attempted.

To detect the antidiuretic hormone in ultrafiltrates of toxæmic blood, Anselmino and Hoffmann made use of the well-known fact that pituitrin, while temporarily inhibiting the excretion of water by the kidney, exerts relatively little effect on the excretion of electrolytes. During the period of inhibited water excretion the concentration of chloride in the urine accordingly

<sup>1</sup> Received January 12, 1934.

rises, to fall again when diuresis sets in. Using fasting rabbits, Anselmino and Hoffmann introduced 90 c.c. of water into the stomach through a catheter, and at the same time injected 10 c.c. of ultrafiltrate from toxæmic blood under the skin. They then collected the urine at half-hourly intervals, measured its volume and determined its chloride content. Their paper is illustrated by diagrams, derived from four cases of toxæmia, which show a fall in volume and a rise in chloride concentration, and they state that similar curves were obtained in all of twenty-four cases of toxæmia in which oedema was present. In control rabbits injected with ultrafiltrates from normal blood they observed a prompt diuresis with a fall in chloride concentration. By comparing their curves with others obtained by injecting known doses of pituitrin they estimated that the antidiuretic content of toxæmic blood ranged between 0.002 and 0.008 Voegtlin units<sup>2</sup> of pituitrin per c.c.

At the beginning of the present investigation the procedure described by Anselmino and Hoffmann was followed as closely as possible. Collodion membranes were prepared which permitted the rapid collection of large quantities (up to 100 c.c. or more) of protein-free ultrafiltrate from plasma (7). Pituitrin was found to pass freely through these membranes. Blood was obtained by aspiration from the antecubital vein into freshly prepared 4.5 per cent. sodium citrate solution (1 c.c. to 20 c.c. of blood) and was centrifugalized immediately. The separated plasma was acidified with normal acetic acid (1 c.c. to 20 c.c. of plasma) and ultrafiltered without delay. The ultrafiltrate was stored in a refrigerator overnight, and was neutralized with normal NaOH solution immediately before use.

The rabbit, though convenient, is by no means an ideal animal on which to study diuresis, and Anselmino and Hoffmann admit that many may have to be rejected before suitable rabbits are obtained. In the hands of the writers the rabbit method has failed to yield satisfactory results. The normal range of hydration in the fasted rabbit is apparently so wide that 100 c.c. of water often fails to cause diuresis; and when extra water is left in the cage overnight the animal often imbibes so unwisely that either diarrhoea follows or the experiment is begun on an animal which is already exhibiting a brisk diuresis. In the latter event the excretion of chloride often falls so low that accurate or duplicate analysis is difficult. In addition the frequent contamination of the urine with mucus and gelatinous material—the urine often clots on standing—renders difficult both measurements of volume and subsequent analysis. The results obtained in these unsatisfac-

<sup>2</sup> With the exception of Pitressin (Vasopressin), commercial pituitary extracts are standardized by the guinea-pig uterus method, that is, in terms of their content of oxytocic principle. It has been shown that the ordinary methods of preparation do not effect any selective extraction of the pressor, antidiuretic, and oxytocic principles; consequently standardization in terms of pressor or antidiuretic units is unnecessary. The standard which is internationally recognized is a powder, of which 0.5 mg. contains one unit. The Voegtlin unit is the same as this international unit.

tory circumstances are shown in Table I. Little or no significance can be attached to them, although it appears that the rabbit method is sufficiently sensitive to detect pituitrin in the dilutions in question.

TABLE I  
*Experiments with Rabbits*

Specimen tested.	Number of experiments.	Result.		
		Negative.	Positive.	Doubtful.
Toxaemic ultrafiltrate	23 (8 cases)	13	2	8
Normal ultrafiltrate	8	6	1	1
Ultrafiltrate from plasma + pituitrin (0.002 unit per c.c.)	4	0	3	1

In assessing the above results the volume of urine excreted has been ignored as conveying no useful information, and attention has been confined to the chloride concentration curves. A positive result has been recorded wherever a rise in chloride concentration has been established by two or more points on the curve. Where evidence of concentration has rested on a single reading the result has been classified as doubtful.

In most instances the chloride concentration was determined every fifteen minutes after injection of the ultrafiltrate.

The method was therefore abandoned in favour of the following procedure, which is essentially the process introduced by J. H. Burn (3) for the assay of the antidiuretic principle in pituitary extracts. A measured quantity of water (5 c.c. per 100 grm. body-weight) was introduced into the stomach of a fasting rat through a small gum-elastic catheter. Immediately afterwards a measured volume (1.0 c.c. per 100 grm.) of the suspected ultrafiltrate was injected subcutaneously. Three other rats were treated in the same way with as little delay as possible, and the four animals were placed in a metabolism cage resting on a large glass funnel, which drained into a 25 c.c. measuring cylinder. A second group of four rats was similarly treated, using either control ultrafiltrate prepared from normal blood or normal saline. The total volume of urine excreted was measured every fifteen minutes until diuresis had subsided. After an interval of one clear day the experiment was repeated, but the two groups of rats were reversed. When the amount of available ultrafiltrate permitted, several groups of rats were used. From the data obtained the interval of time elapsing between the beginning of the experiment and the peak of the diuresis has been ascertained by means of a simple calculation (v. Burn, *loc. cit.*). In rats which receive no pituitrin the peak should occur within 50 to 90 minutes after the introduction of water into the stomach. If a filtrate containing pituitrin is used, the onset of diuresis is delayed and its peak postponed beyond the normal upper limit. According to Burn the smallest amount of pituitrin which can be consistently demonstrated by this technique is about 0.001 international units per 100 grm. of rat.

I. *Experiments with Pituitrin*

These were planned to ascertain whether the rat method is sufficiently sensitive for the present purpose. Pituitrin (Parke Davis) was added to normal citrated plasma in the proportion of 0.002 unit per c.c. The plasma was then acidified, submitted to ultrafiltration, and finally neutralized immediately before use. The neutralized ultrafiltrate was injected into rats in the proportion of 1 c.c. per 100 gm. of rat. The results are collected in Table II. It will be seen that the peak of diuresis was postponed beyond the normal upper limit in twenty-seven out of thirty-four experiments. Of the remaining seven readings which fall within normal limits, six were

TABLE II  
*Experiments with Rats*

Ultra-filtrate No.	Number of observations.	Age of filtrate.	Peak of diuresis (minutes).		
			Highest (normal 90).	Lowest (normal 50).	Mean (normal 70).
1 <sup>3</sup>	6 (i.e. 24 rats)	24 hours	202	147	170
1 <sup>3</sup>	6	3 days	150	111	126
2	6	24 hours	198	126	164
2	4	3 days	118	93	104
3	3	24 hours	124	112	116
4	6	24 "	85	59	73
5	3	24 "	131	83	112

Effect of ultrafiltrates derived from normal plasma to which pituitrin had been added (0.002 unit per c.c.) on water diuresis in rats.

obtained on the same day with a single specimen of ultrafiltrate (Table II, No. 4). The ultrafiltrate was freshly prepared, and no explanation of this single consistently negative result was discovered. It is evident from Table II that ultrafiltrates obtained from plasma + pituitrin deteriorated appreciably during the interval of one clear day which was unavoidable when experiments were repeated with the same rats. In spite of this deterioration, filtrates kept for three days still caused consistent postponement of diuresis, the average peak in these repeated experiments occurring at 117 minutes. It may therefore be concluded that Burn's method is sensitive enough to detect pituitrin in ultrafiltrates from plasma containing 0.002 unit per c.c.—that is in the minimum (or one-fourth of the maximum) concentration which is alleged by Anselmino and Hoffmann to occur in the mildest cases of pre-eclamptic 'toxaemia'.

II. *Observations on Toxaemic Ultrafiltrate*

In selecting cases for investigation uncomplicated albuminuria was not considered evidence of pre-eclamptic toxaemia. Every patient studied (v. Appendix) displayed, in addition to albuminuria, visible pitting oedema and, with one exception (Case 4), a systolic blood-pressure of between 140

<sup>3</sup> Dr. Burn kindly standardized the pituitrin used in preparing this ultrafiltrate against the standard international powder, by the antidiuretic method and also by the oxytocic method.

and 190 mm. Hg. The series included three cases of eclampsia. In seven instances the urine had been tested before the onset of symptoms and had been found to contain no albumen. Cases of chronic nephritis, aggravated by pregnancy, have been excluded from the series. Ultrafiltrates were obtained from 13 cases of toxæmia and 38 observations, each based on four rats, were made with these filtrates. The complete results are appended to the case summaries (*v. Appendix*). In 19 of these experiments, based on 10 specimens of blood, the filtrate was injected into rats within 24 hours of

TABLE III

Material injected.	Total number of experiments.	Peak of diuresis within or below normal limits.	Peak of diuresis delayed beyond upper normal limits.
<i>Group I</i>			
Ultrafiltrates from normal plasma + pituitrin (0.002 unit c.c.)	34	7	27
<i>Group II</i>			
Ultrafiltrates from toxæmic plasma	38 (13 cases)	34	4
<i>Group III</i>			
Ultrafiltrates from normal plasma (21 expts.), and normal saline (23 expts.)	44	39	5

Relative effects on water diuresis in the rat of ultrafiltrates derived from 'toxæmic' plasma, from normal control plasma, and from normal plasma + pituitrin.

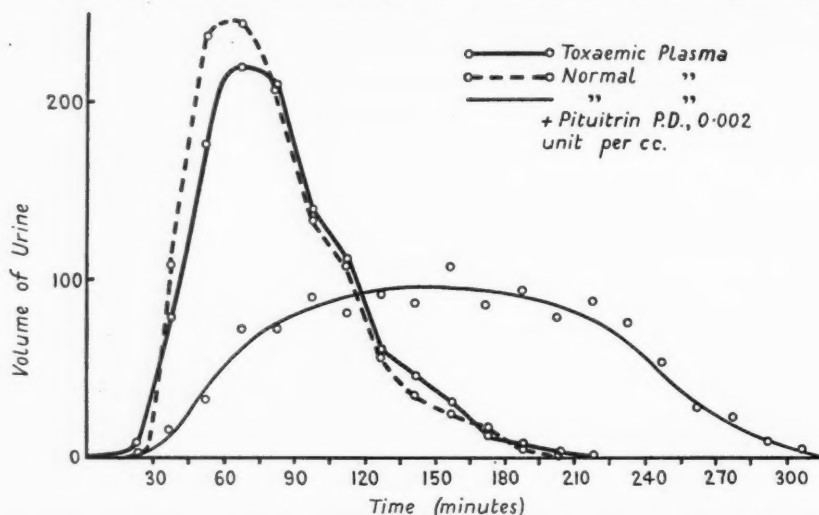
obtaining the plasma. The remaining 19 were mainly repeated experiments on the same ultrafiltrates, with an interval of one clear day. There was no significant difference, however, between the effect of the fresh and older ultrafiltrates on diuresis, the average peak with fresh filtrates occurring in 72 minutes, and with older filtrates in 76 minutes. Considering the results as a whole, the peak of diuresis fell within or below the normal range in 34 of the 38 experiments (Table III). The four exceptions in which diuresis was postponed were isolated observations, one on fresh, three on older filtrates, from four different patients. None of these four readings was confirmed by earlier or simultaneous observations on other groups of rats.

### III. Experiments with Control Ultrafiltrates or Normal Saline

Forty-four control experiments were performed. In 21 of these, ultrafiltrates of blood from normal adult subjects, or from various irrelevant diseases such as congestive heart failure and gastric ulcer, were employed. In the remaining 23 the rats received normal saline solution (1.0 c.c. per 100 grm.) instead of ultrafiltrate. In this control group the peak of diuresis fell within or below the normal range in 39 experiments and was postponed in the remaining five (Table III).

The essentially negative results of the investigation are further illustrated

in the diagram. In constructing this diagram the volumes of urine excreted in each 15-minute interval in all the 38 experiments in which toxæmic ultrafiltrate was used have been massed together. The resulting curve therefore represents the mean effect on the water diuresis curve of injecting ultrafiltrates from the blood of 13 cases of toxæmia into 152 rats. The results of the control and pituitrin experiments have been similarly treated. It is



Mean effect on water diuresis curve of ultrafiltrates derived from toxæmic plasma, from normal plasma, and from normal plasma + pituitrin. The curves are derived from the pooled data mentioned in the text.

quite clear from this diagram that the injection of toxæmic ultrafiltrate in the dose of 1.0 c.c. per 100 grm. of rat has not caused any significant delay in the excretion of extra water in that animal. On the other hand the injection of filtrate derived from plasma to which pituitrin had been added in the proportion of 0.002 unit per c.c. has caused a marked flattening of the diuresis curve. The absence of a sharp peak on the latter curve is due to the fact, referred to above, that the effect of pituitrin varies in intensity from rat to rat and from day to day.

The possibility that the cases studied were all milder examples of toxæmia than the mildest cases studied by Anselmino and Hoffmann must be considered. It seems, however, very unlikely. It may be concluded that, if an excess of antidiuretic principle is present in the blood in toxæmia, its concentration must be considerably lower than Anselmino and Hoffmann suggest. It would seem that further evidence is required before the pituitary origin of eclampsia can be regarded as established.

The writers are indebted to Professor Arthur Ellis, under whose direction the investigation was pursued, and Professor J. H. Burn for much helpful advice, to the Obstetric Surgeons of the London Hospital, Queen Mary's

Hospital, Stratford, and the City of London Maternity Hospital, for clinical material, and to the Trustees of the Research Fund of the London Hospital for a grant towards the expenses of one of us (C.W.). The work has been done under the tenure of a Beit Memorial Fellowship.

### Summary

A method which is capable of detecting the antidiuretic hormone of the pituitary after addition to blood-plasma in a dilution of 0.002 international unit per c.c., has failed to reveal the presence of the hormone in ultrafiltrates derived from the plasma of ten cases of pre-eclamptic toxæmia of pregnancy and three cases of eclampsia with oedema.

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### APPENDIX

#### Summary of Case Records

*N.B.* The results on which the above paper is based are appended to the end of each summary. For example, Case 1, 24 hours—87 (60) means that ultrafiltrate was used within 24 hours of obtaining the blood, and that the peak of diuresis occurred 87 minutes after injection of ultrafiltrate in one group of four rats, as against 60 minutes in the case of the control group.

*Case 1.* S.D. aged 34. *Severe pre-eclamptic toxæmia.* Admitted in 38th week with gross oedema of legs, trunk, and breasts, and gross albuminuria; blood-pressure 150 mm. Hg. syst. 110 mm. Hg. diast. *Results.* 24 hours—87 (60), 4 days—87 (92); (2nd spec.) 24 hours—103 (92).

*Case 2.* A.S. aged 25. *Pre-eclamptic toxæmia; triplets.* Two previous pregnancies; uncomplicated albuminuria during second. Last menstrual period April 21st 1931; urine clear until Jan. 6th 1932; then albuminuria,  $\frac{9}{10}$  deposit on standing; X-ray-triplets; pitting oedema  $\frac{1}{2}$  inch deep over both ankles; blood-pressure 140/100. Blood taken at onset of first stage of labour. *Results.* 48 hours—102 (110).

*Case 3.* V.L. *Eclampsia.* One previous pregnancy (normal). Last menstrual period June 14th 1931; urine clear until Jan 8th 1932; patient then admitted with 10 days' history of swelling of feet; 4 fits on day of admission; slight oedema of ankles; blood-pressure 155/125. *Results.* 24 hours—90 (122); 3 days—127 (84).

*Case 4.* A.H. aged 30. *Eclampsia.* First pregnancy; admitted in 7th month with 19 days' history of swelling of ankles and face and albuminuria; 9 fits on day of admission; gross albuminuria, slight pitting oedema of ankles; blood-pressure 130/90. *Results.* 3 days—64 (61), cerebrospinal fluid—81 (50); 5 days—64 (59), cerebrospinal fluid—75 (67).

*Case 5.* G.A. aged 39. *Severe pre-eclamptic toxæmia.* Four previous pregnancies, all normal. Last menstrual period July 30th 1931; urine clear until March 16th 1932, when albuminuria was first observed, together with swelling of face and ankles. Admitted April 7th 1932 with gross oedema of legs and face; blood-pressure 170/105; albuminuria. *Results.* 2 days—90, 86 (58); 4 days—74, 52 (75); second sample of blood, 24 hours—42 (64); 5 days—67 (45).

*Case 6.* A.H. aged 36. *Severe pre-eclamptic toxæmia.* First pregnancy; albuminuria and oedema of legs first appeared at 30th week; admitted two weeks later with pitting oedema of ankles and albuminuria; blood-pressure 190/110. *Results.* 24 hours—71, 70 (54); 48 hours—47, 47 (55).

*Case 7.* W.K. aged 24. *Eclampsia.* First pregnancy; last menstrual period Sept. 17th 1931; admitted April 17th 1932 with 11 days' history of swelling of legs and face and 3 days' history of severe headache; 5 fits on day of admission; history of epileptiform seizures during infancy. Oedema of face, arms, legs, and feet; blood-pressure 180/120; urine  $\frac{7}{8}$  deposit albumin on boiling. (*Comment*—The albuminuria, oedema, and hypertension exclude the diagnosis of epileptic convulsions.) *Results.* 12 hours—79, 54 (75, 72); 3 days—77, 64 (81, 48).

*Case 8.* S.S. *Severe pre-eclamptic toxæmia.* A patient with very gross oedema of the lower limbs, abdominal wall, and breasts, and albuminuria ( $\frac{1}{2}$  to  $\frac{3}{4}$  deposit on boiling). First seen on day of labour (full term); blood-pressure then 170/110. Blood taken on following day. *Results.* 4 days—62 (51).

*Case 9.* L.H. aged 26. *Mild pre-eclamptic toxæmia.* First pregnancy; last menstrual period Dec. 29th 1931; urine clear until July 25th 1932; albuminuria and swelling of feet and face noticed Sept. 5th 1932; blood-pressure then 170/100. Blood taken Sept. 15th; blood-pressure then 160/100; slight oedema of feet. *Results.* 24 hours—89, 87 (104, 99).

*Case 10.* E.D. aged 28. *Moderately severe pre-eclamptic toxæmia.* First pregnancy; full term; admitted in first stage of labour with gross oedema of legs; albuminuria ( $\frac{1}{4}$  deposit on boiling); blood-pressure 160/80. *Results.* 24 hours—75, 59 (62).

*Case 11.* R.C. aged 27. *Recurrent pre-eclamptic toxæmia.* Toxæmia during previous pregnancy two years ago, with albuminuria and hypertension (210/120), terminating in stillbirth at 28th week. Last menstrual period Aug. 7th 1932; urine clear until Jan. 17th 1933; blood-pressure Nov. 1932—125/80, Jan. 10th 1933—120/80, April 26th 1933—150/100; moderately gross oedema of legs. *Results.* 3 days—89, 61 (96).

*Case 12.* L.A. aged 28. *Mild pre-eclamptic toxæmia.* Two previous pregnancies ending in unexplained abortion in 4th and 5th months respectively. Admitted full term in first stage of labour, with 2 months' history of swelling of legs and headaches; slight albuminuria; moderate oedema of ankles; blood-pressure 165/100. *Results.* 24 hours—67, 48 (71).

*Case 13.* B.S. aged 36. *Severe pre-eclamptic toxæmia.* Second pregnancy; swelling of feet noticed at 28th week, with albuminuria ( $\frac{1}{10}$  deposit on boiling). Blood taken 10 days later; blood-pressure then 180/105; moderate oedema of ankles. *Results.* 24 hours—65, 74, 78 (89); 3 days—96, 86 (78).

## THE RESPIRATORY EXCHANGE DURING EXERCISE IN HEART DISEASE. III<sup>1</sup>

By MAURICE CAMPBELL

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THE general causes of dyspnoea in heart disease are well recognized, but the exact mechanism is less fully understood. Attempts to elucidate this have been made in two earlier papers (6, 7), in the second of which the respiratory exchange and pulmonary ventilation of three patients were measured during and after exercise. Similar observations have now been made on sixteen patients.

Earlier work has been discussed in these papers, and it is agreed that the metabolism is increased to about the same extent as in the normal, but that the difficulty is in maintaining an adequate exchange of oxygen and carbon dioxide between the muscles and the outside air. There are three main steps in the process: (1) the movement from the muscles to the lungs and from the lungs to the muscles (the circulation-rate); (2) the passage of the gases from the capillaries to the alveolar air and the reverse; and (3) the ventilation of the lungs.

The circulation-rate in health, both at rest and during exercise, is now known with reasonable accuracy (9, 17, 19). It has been measured at rest in several varieties of heart disease (2, 10), but the methods are difficult enough to use with patients at rest, and so little has been done in the effects of exercise. Similarly, the alveolar air and the gas content of the blood have been determined in many forms of heart disease (1, 5, 14, 21, 22), but again the methods are difficult enough to use with the subject resting. It is much easier to measure the pulmonary ventilation and expired air during exercise, and it is with these only that we are concerned here.

*Methods.* The exercise chosen was stepping on and off a wooden block, 13 in. high. A lower step would have been more like the exercise of stair climbing, to which most people are accustomed, but data about the pulse-rate, &c., had already been collected for this particular exercise (8), and as the work done is mostly due to raising the body-weight up a particular height, it is easy to express as kilogram-metres.

The patients were tested at two rates—six steps a minute and twelve steps a minute—both being continued for five minutes at a time, since previous experience had shown that after three minutes a condition of equilibrium

<sup>1</sup> Received January 17, 1934.

had almost been reached. Observations were made during ten or fifteen minutes of rest before the exercise, continuously during the exercise, and for ten minutes afterwards, by which time the patient had generally returned to his resting condition. Judged by the oxygen consumption to which it gave rise, the easier exercise of six steps a minute was rather easier than slow walking at  $2\frac{1}{2}$  miles an hour, and the harder exercise of twelve steps about the same as walking something over  $3\frac{1}{2}$  miles an hour (11).

The method used for recording the ventilation and respiratory metabolism was a closed circuit apparatus of the Regnault-Reiset type, with the oxygen admitted by the principle described by Douglas and Haldane (12) and a Krogh spirometer introduced as a side circuit (18). This is less accurate than the Douglas bag method used for each minute separately, but it has the great advantage that the changes can be followed more easily. The subject wore a mask strapped tightly over the mouth and nose, and fitted to the contour of the face closely by an air cushion blown up to the requisite extent. The expired air was led to a mixing chamber, from which samples could be withdrawn to analyse the percentage of carbon dioxide, and passed next through a cylinder containing alternate layers of soda lime and flaked soda to absorb carbon dioxide, and finally through a collapsible rubber bag back to the inspiratory valve. This bag was enclosed in a rigid vessel communicating with a spirometer, the movements of which were recorded on a revolving drum where the minute periods were marked. The rate of breathing was counted on this drum, and the total ventilation read each minute on a dial which recorded the movements of the spirometer in one direction only, thus saving the labour of measuring up the record of these movements. In this way the ventilation was obtained for each minute as long as required. The apparatus with some later modifications has been fully described elsewhere (27).

When a steady state of exercise had been reached the percentage of carbon dioxide in the mixed expired air gave the carbon dioxide output accurately, and after the first few minutes the results agreed closely with those of the Douglas bag method. Even during the period of change at the beginning and the end of exercise an approximate estimate of the carbon dioxide output was obtained. Generally, samples of expired air were analysed directly at the end of the first and fourth or second and fifth minutes of exercise; and taken over mercury into Douglas tubes, which could be analysed later, at the end of the first, second, and third minutes after exercise; and subsequently the samples were again analysed directly at two- or three-minute intervals. Thus the carbon dioxide output was obtained directly for about half the minutes during and after exercise, and for the remaining minutes by interpolation. This was not absolutely correct when changes were taking place rapidly, but any error was minimized by comparing the results obtained in the same way for breathless and healthy subjects, a comparison with the Douglas bag method showing that there was no great inaccuracy.

It was more difficult to get the oxygen intake for each minute separately.

With inspiration the pressure in the circuit fell and oxygen was drawn in, the supply from the cylinder being so arranged that after passing through a meter and a water valve it entered the circuit if the pressure there fell, but bubbled away through a second water valve offering slightly less resistance if the pressure in the circuit remained constant. If deep breaths were taken during one particular minute more oxygen was drawn into the circuit than was used by the subject, and similarly if the breathing was restrained less oxygen was drawn in, so that from minute to minute the oxygen passing through the meter did not record accurately the amount used. But these changes soon adjusted themselves, and in a fifteen-minute period the consumption was accurately recorded. In a five-minute period a fairly accurate result was obtained, and when a subject was breathing regularly and the water-levels had been so adjusted that the resistance to the inflow of oxygen was as small as possible, the results were fairly constant from minute to minute; but for all the values at rest fifteen-minute periods were taken. To some extent this error was avoided by making at least three observations on each subject at each rate of exercise and considering the average, but the oxygen values were levelled out by using smoothed curves where there was any great irregularity from minute to minute.

*Subjects.* Of the sixteen subjects examined, nine had mitral disease, three had mitral and aortic, and four had aortic disease only. In two of the last four the aetiology was syphilitic; in the remainder it was rheumatic. All had normal rhythm except four with auricular fibrillation. The extent to which the heart was affected was more difficult to estimate, but at the time of examination all were able to attend as out-patients, though two with some signs of congestive failure could only just do this and little else.

They had already been divided into four groups:

(i) Only slight dyspnoea on exertion; able to do ordinary work—Cases 7 and 29.

(ii) More obvious dyspnoea on exertion, only able to do light or clerical work. This included five cases.

(iii) Dyspnoeic on walking, unable to work; only slight signs of congestive failure, though sometimes these had been more obvious before treatment with digitalis. This included five cases.

(iv) With moderate congestive failure; dyspnoeic on slightest exertion. Cases 12 and 31 had moderate congestive failure, and were only just able to attend as out-patients, and Cases 23 and 35 had to be admitted to hospital for congestive failure a few months later.

As the groups were small (i) and (ii) have been taken together for most purposes as Group A, (iii) and (iv) together as Group B.

### *Experimental*

*Pulmonary ventilation.* The ventilation at rest varied between 4.1 and 5.4 litres per square metre of surface area per minute; this was chosen as the most

accurate measure of comparison since some allowance was needed for the variation in size and weight. The average for the normals was 4.2 litres, and those with heart disease were mostly in the upper normal range; those where it was above 5.0 litres were generally the more breathless. In an earlier series, where most were, or had recently been, in-patients because of their hearts, the ventilation was higher (6). There was no difference between the mitral and aortic groups at rest or at exercise, so that they have been taken together.

TABLE I

*Percentage Increase in Pulmonary Ventilation during and after Exercise*

Pulmonary ventilation at rest (litres).		Percentage increase each minute.									
		Exercise.					After exercise.				
		1	2	3	4	5	1	2	3	4	5
		6-10									
Exercise 6 steps.											
Normal	6.9	178	201	200	202	209	174	138	118	108	108
Heart disease	6.9	142	175	191	200	206	177	146	123	114	111
Exercise 12 steps.											
Normal	6.8	194	238	263	288	296	237	156	131	117	106
Heart disease	6.2	170	213	245	256	266	218	178	152	131	124

The ventilation during exercise showed about the same percentage increase as in the normals (see Table I); it was therefore a little higher during exercise and after, as it had been at rest. Similar results were obtained by Peabody (24). At the easier exercise the difference from the normal was slight in Group A, but considerable in Group B. At the harder exercise owing to the absence of the most breathless patients there was less distinction between the two subdivisions. Results for each group expressed as litres per square metre surface area are shown in Fig. 1.

Both the increase at the beginning of exercise and the return to the resting condition afterwards took place more slowly than normally. At the harder exercise, especially in Group B, the percentage increase in ventilation was less than normal even at the end of exercise, i.e. the usual delay in reading an adequate ventilation continued, with the result that the increase after the exercise was greater and continued for longer. A few patients (e.g. Cases 27, 32, and 35 at six steps) increased their ventilation more than the average normal, even as a percentage increase; but none showed a much greater increase, such as was found in some men with effort syndrome and chronic bronchitis (26).

This increased ventilation might be a factor in causing dyspnoea, but so slight that it would be of no importance normally, and the real cause of dyspnoea must be looked for elsewhere.

*The rate of breathing.* There were more significant differences as regards the rate and depth of breathing. Even at rest the rate of the patients with heart disease was slightly faster. With exercise this became more important, and in the last minute of the easier exercise the average rate of the patients was twenty-six as compared with nineteen for the normals, which meant that the breathing was more shallow, and so that the effective alveolar ventilation was less.

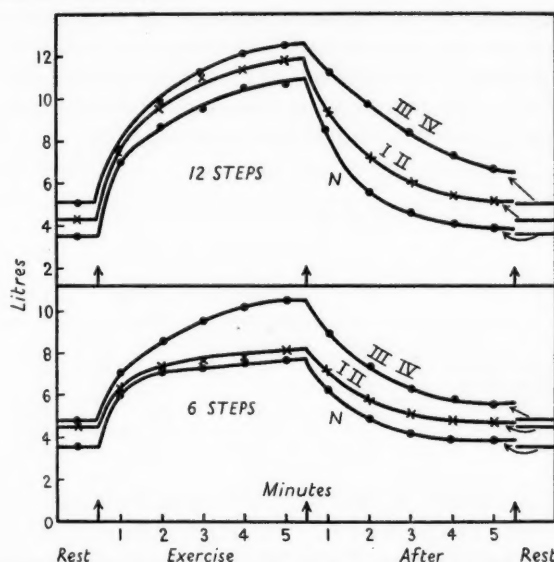


FIG. 1. The pulmonary ventilation during and after exercises of six steps (below) and twelve steps (above).

Three curves are shown at each rate of exercise—one for the normals and two for the patients with heart disease, divided into Groups I and II, and Groups III and IV. The ventilation is expressed as litres per square metre surface area per minute, and is shown for one minute at rest, for five minutes of exercise, and for five minutes afterwards (see text).

TABLE II  
*The Rate of Breathing with Exercise*

	Rest.	Exercise 6 steps.			Rest.	Exercise 12 steps.		
		3rd min.	5th min.	3rd min. after.		3rd min.	5th min.	3rd min. after.
Normals	16	19	19	17	16	21	23	17
Patients with heart disease	18	24	26	20	15	23	24	19
Patients: Group A	16	19	20	17	14	21	22	17
"    Group B	21	29	30	24	18	27	28	22
Aortic incompetence	15	20	21	15	13	19	20	15
Mitral stenosis	23	29	31	26	18	28	29	24

Here and subsequently the patients have been divided (*a*) according to the severity of the disease into Groups A and B, and (*b*) according to the nature of the valvular defect, into those with aortic disease and those with mitral disease only. In the more breathless (Group B) the rate was

faster at rest and much faster during and after exercise; in the less breathless (Group A) it was normal (see Table II). In those with aortic incompetence the average figures were normal, but in those with mitral stenosis they were increased by more than 50 per cent., both during and after exercise.

With the harder exercise the results were less striking, evidently because the more breathless were unable to do the twelve steps a minute. This was shown by comparing the rate of breathing after the easier exercise of those who were tested at both rates, and of those who were not tested at the faster rate. In the former the average rate was seventeen, and in the latter thirty-two. Moreover, in the two patients who tried the faster rate and had to stop, the rate had already risen to forty and forty-four.

TABLE III

*The Depth of Breathing with Exercise*

	Rest.	Exercise 6 steps.		Exercise 12 steps.	
		3rd min. exercise.	3rd min. after.	3rd min. exercise.	3rd min. after.
Normals	430	725	485	850	525
Patients with heart disease	380	550	435	660	495
Patients: Group A	400	570	430	745	510
"      Group B	340	500	390	535	495
Aortic incompetence	450	640	560	810	620
Mitral stenosis	310	470	350	555	395

*The depth of breathing.* As the rate of breathing was faster in most patients with heart disease, and as the total ventilation was not much increased, the depth of breathing was less. Table III shows some difference at rest and more during exercise. It was more shallow in Group A and much more shallow in Group B, where, with the harder exercise, the depth was only increased by 195 c.c. instead of by 420 c.c., as with the normals. Those with aortic disease showed little tendency to shallow breathing, but those with mitral stenosis showed it at rest and during exercise.

This shallow breathing was a real drawback, because a greater proportion of each breath was wasted in moving the air of the dead space in the trachea and bronchi, and the true alveolar ventilation was diminished. Taking the third minute of the easier exercise as an illustration and assuming a dead space of 140 c.c.—an average figure—the effective alveolar ventilation of the normal was 11.2 litres for a total pulmonary ventilation of 13.8 litres (81 per cent.). For Group B the effective ventilation was 10.4 litres for a total ventilation of 14.4 litres (72 per cent.). Actually a greater total ventilation was needed for a smaller effective alveolar ventilation, and this was certainly one factor in producing their dyspnoea, especially in those with mitral stenosis. During the third minute after exercise the same result was observed to a greater extent, the effective alveolar ventilation of the normals being reduced from 8.2 to 5.8 litres, and of those with heart disease (Group B) from 9.3 to 5.5 litres.

When the exercise was twelve steps a minute the results were similar, but no more striking, since only the more fit patients were able to take part. During the third minute of exercise the effective alveolar ventilation of the normal was 15.0 litres for a total pulmonary ventilation of 17.9 litres (84 per cent.); the corresponding figures for all the cardiac patients being 12.0 from 15.2 litres (79 per cent.); and for those of Group B 10.6 from 14.4 litres (74 per cent.). The real reduction would be rather more than shown because actually the dead space increases with exercise, and no extra allowance has been made for this.

It is interesting to compare the depth to which the breathing was increased by these exercises with the maximum depth to which it could be increased, i.e. the vital capacity. The average figures for the sixteen cases of this paper are shown in Table IV. Wentworth and Peabody (25), Hewlett (15), and Myers (23) have emphasized the importance of the vital capacity.

TABLE IV  
*Percentage of Vital Capacity Used during Exercise*

	Vital capacity (percentage of normal).	Maximum depth of breathing expressed as percentage of V.C.	
		Exercise 6 steps.	Exercise 12 steps.
Normals	95	17	20
Patients with heart disease	65	28.5	33
Patients: Group A	76	27	30
„ Group B	53.5	29.5	38
Aortic incompetence	73	29.5	32
Mitral stenosis	57	27.5	34

Several of the patients used 40 per cent. of their vital capacity for the harder exercise, and the average was 33 per cent., although the controls, who breathed more deeply than the others, only used 20 per cent. of their vital capacity. This was, no doubt, an important factor in their sensation of breathlessness.

Group B used 38 per cent. of their vital capacity with the harder exercise against 30 per cent. for Group A, though the individual figures were variable. The difference in their percentages was not as great as in the actual depth of breathing, because the capacity for increasing the depth of breathing was nearly as much diminished as the vital capacity itself.

*The percentage of carbon dioxide in the expired air.* The percentage of carbon dioxide in the expired air of those with heart disease was always lower than normal. At rest, since their total metabolism was normal, this was due to the rather higher pulmonary ventilation and often to the relatively poor effective ventilation caused by rapid shallow breathing. During exercise this rapid shallow breathing was more important, and in addition the ventilation increased more slowly during the first minutes of the exercise. There was a lower output of carbon dioxide, especially at the start of exercise, because of its lower percentage in the expired air without a corresponding increase in the volume. As the extra metabolism due to the work was

never less and sometimes rather more than normal, this meant a retention of carbon dioxide in the blood and body fluids, and was another cause of their dyspnoea.

TABLE V  
*The Percentage of Carbon Dioxide in the Expired Air*

	Carbon dioxide percentage.		
	At rest.	In 3rd minute of exercise.	
		6 steps.	12 steps.
Normals	3.39	4.25	4.36
Patients with heart disease	3.07	3.62	3.96
Patients: Group A	3.36	4.11	4.39
"      Group B	2.84	3.24	3.62
Aortic incompetence	3.35	3.97	4.40
Mitral stenosis	2.82	3.23	3.48

In Group A the results were substantially normal (see Table V), as might be expected, since six and twelve steps corresponded to very slow and moderate walking which generally did not cause dyspnoea for these patients. On the other hand, in Group B, where there was dyspnoea even on walking, the results differed greatly from the normal, even at these easy exercises. On the whole these effects were greater in the patients with mitral stenosis, again probably because of their tendency to rapid shallow breathing.

The carbon dioxide in the alveolar air can be calculated from these data, assuming a constant dead space proportional to the size of each patient. These figures must only be used for comparison between those with heart disease and the normals, since the increase of the dead space with the deeper breathing of exercise makes the apparent increase of the normal rather too high. The alveolar air was substantially normal at rest and during the two exercises for Group A, 4.56, 5.02, and 5.19 per cent. of  $\text{CO}_2$  against 4.89, 5.18, and 5.28 for the normals; but in Group B it was low at rest and there was no apparent increase with exercise, 4.23, 4.15, and 4.22. Two possible explanations are that the transference from the venous blood to the alveolar air is obstructed so as to prevent the usual equilibrium; or that even with these easy exercises lactic acid has been produced and is acting as part of the respiratory stimulus.

*The respiratory exchange.* The metabolic changes will not be discussed in detail since there is little to add to the conclusions of an earlier paper on a small number of cases (7). The total metabolism did not differ much from the normal, but allowing for the smaller size and weight of the patients it was rather greater for the work done in raising their weight up the steps, because they were less practised at the exercise and less able to do it with a minimum of muscular movements. Fig. 4 shows that the extra oxygen used increased almost regularly with the work done, and that the patients and normals behaved in practically the same way. This agrees with the conclusions of previous workers (3, 4, 20).

The work has been expressed as kilogram-metres per minute by multiplying the height of the step (0.325 metre) and the number of steps per minute and the weight of the patient (neglecting any extraneous movements which were not capable of accurate measurement). As 1,000 kilogram-metres are equivalent to 2.35 calories, and as one litre of oxygen gives about 4.83 calories, the oxygen needed as the actual physical equivalent of the work done is 0.157 c.c. per step per kilogram of body-weight. It is therefore possible to compare the extra oxygen actually used with the oxygen needed as the physical equivalent of the work done, i.e. the 'efficiency'. For the normal this rose

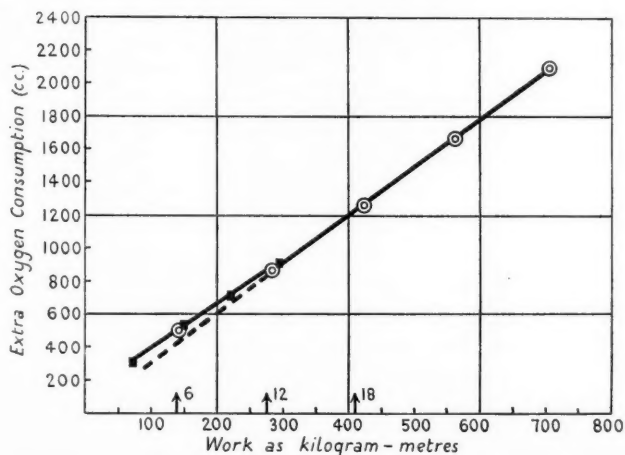


FIG. 2. The extra oxygen consumption (c.c. per minute) plotted against the work done, this being expressed as kilogram metres per minute.

The relationship is expressed by a line that is almost straight. The results for normals are shown by circles, and for patients with heart disease by squares. There was little difference between the normals and the patients with heart disease. The 'efficiency' was slightly less at the lower rates of exercise.

The extra oxygen consumption has been obtained by deducting the oxygen used per minute at rest from the oxygen used per minute during exercise. The work done has been calculated by multiplying the height through which the body was raised each minute (in metres) by the body-weight (in kilograms) (see text). Three points have been marked to correspond to the work done during exercises of 6, 12, and 18 steps by an average man of 70 kilograms.

from 13.1 to 16.3 per cent. as the exercise was increased from six steps to twenty-four steps, and for the patients with heart disease from 11.3 to 13.6. This percentage efficiency only applies to this particular stepping exercise. With a specially constructed bicycle ergometer working against measured resistance it may be 25 per cent. (18). The dyspnoea of heart disease is not therefore produced by the actual oxygen requirements being different in any way.

Slightly less oxygen was used during the exercise and slightly more after it was over, i.e. the 'oxygen debt' (16) was rather greater; but the difference was very slight and would certainly not be an important factor in

their dyspnoea. This makes it unlikely that lactic acid was responsible for the low carbon dioxide in the expired air.

The output of carbon dioxide showed rather more significant changes than the intake of oxygen. Table VI shows this, expressed as c.c. per kilogram

TABLE VI  
*Extra Carbon Dioxide Expired with Exercise (Expressed as c.c. per kg. Body-weight)*

Extra carbon dioxide (c.c. per kg. body-weight.								
		Separate minutes.				Total.		
		During exercise.			After exercise. 2nd min.	During exercise.	After exercise.	During and after.
		1	2	3				
Exercise 6 steps.								
Normals		3.4	4.2	4.6	1.6	22.0	6.7	28.7
Patients:	Group A	2.6	4.4	4.9	2.1	23.4	8.5	31.9
„	Group B	2.2	4.1	5.2	3.3	23.0	13.0	36.0
Exercise 12 steps.								
Normals		4.6	6.7	7.9	2.3	36.8	11.2	48.0
Patients:	Group A	5.1	8.1	10.1	4.2	44.0	17.2	61.2
„	Group B	2.7	5.7	7.3	5.1	33.3	21.9	55.2

body-weight to allow for size, for the periods when there were most differences. There was a lower output of carbon dioxide, owing to its lower percentage in the expired air without a corresponding increase in the volume, especially in the first one or two minutes of exercise; and the lag in getting rid of carbon dioxide then would lead to some retention in the blood and body fluids, which would act as an extra respiratory stimulus. With the easier exercise this lag was only noticeable in the first minute, but with the harder exercise it was still noticeable in the second minute for Group B. Correspondingly the output after the exercise was much increased, and for Group B after the harder exercise was about double the normal.

Taking Group B and the easy exercise as an example, there was a retention of 13.0 c.c. per kilogram body-weight at the end of the exercise. In the normal there was 6.7 c.c., so that the excess was 6.3 c.c. per kilogram, or about 300 c.c. As a 100 c.c. of blood contains 40 c.c. of carbon dioxide, the 5 litres of blood would contain 2,000 c.c., and if even half the 300 c.c. was in the blood and half in the other body fluids, it would be enough to act as an additional respiratory stimulus. This suggests the importance of the direct determination of the alveolar air during exercise in patients with heart disease. This retention of carbon dioxide is one factor in the dyspnoea of heart disease.

#### Conclusions

In patients with heart disease the percentage increase of the pulmonary ventilation during easy exercise was normal. The increase took place more

slowly at the beginning and lasted longer afterwards. At rest the ventilation was rather greater relatively to their size, and this remained true during and after exercise.

The breathing was faster and more shallow, especially during exercise. This rapid shallow breathing was more characteristic of mitral stenosis, and of those who were most breathless. The effective alveolar ventilation was therefore a smaller percentage of the total pulmonary ventilation. Both these factors would tend to cause dyspnoea, but alone they would not do so in a normal subject.

In spite of the shallow breathing the percentage of the vital capacity which was needed, even during these easy exercises, was greater than normal (33 against 20 per cent.). No doubt this was an important factor in the sensation of breathlessness.

The percentage of carbon dioxide in the expired air was lower than normal, and this difference was increased during exercise, especially in those with mitral stenosis and in those who were short of breath with easy walking.

The output of carbon dioxide, especially in the first minute of exercise, was less than normal, and this lag would be responsible for some degree of hyperpnoea during the remainder of the exercise and after. The utilization of oxygen was almost the same as normal, and the oxygen debt at the end of exercise was less than this retention of carbon dioxide. The pulmonary ventilation and the intake of oxygen did not differ greatly from the normal in these patients with heart disease.

It seems probable that the more rapid shallow breathing with a smaller effective alveolar ventilation and the lower percentage of carbon dioxide expired were factors in the production of their dyspnoea. But the smaller margin between their depth of breathing and their maximum vital capacity appeared a more important factor in their sensation of dyspnoea.

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## THE EFFECTS OF BODILY REST, MUSCULAR ACTIVITY AND INDUCED PYREXIA ON THE VENTRICULAR RATE IN COMPLETE HEART-BLOCK <sup>1</sup>

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With Plate 20

IN healthy people bodily rest, physical activity, metabolic processes, emotion, and environment have a profound effect on the rate of the heart-beat. It is undoubted that easy and spontaneous fluctuations in the rate of the heart are for the most part initiated and controlled by variations in nervous tone. In complete heart-block the independent ventricular rhythm is deprived of the labile and sensitive supervision inherent in the sino-auricular node. This disability has been stressed by numerous writers (8, 21, 24, 28) though few are so dogmatic as Vaquez (35) who formed the opinion that the bradycardia of complete block was invariable and quite unalterable by those influences which ordinarily retard or accelerate the pulse. As judged by the reactions to adrenalin (18) and atropine (17) it has been possible to show in the blocked heart of man that the auricular and ventricular rhythms are each independently responsive to the gross and abrupt alterations in nervous tone thus artificially induced.

In the present paper it is proposed to study the effects of such alterations in the rate of the ventricles as may be induced by a prolonged bodily rest, by muscular activity and by a sudden bout of pyrexia in patients suffering from complete heart-block.

### *The Auricular and Ventricular Ranges during Bodily Rest.*

Detailed observations on the rate of auricles and ventricles have been made on eleven of fourteen cases of complete heart-block (Cases, 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, and 13). Two to three hours after breakfast the patient was brought from his bed in a wheeled chair to the electrocardiograph department and allowed to rest comfortably in a position of maximum ease on a couch for an hour or more, at the end of which time tracings of the heart's action were secured. Frequent visits had previously rendered him

<sup>1</sup> Received February 16, 1934.

TABLE I

Case No. and initials.	1. Mrs. T.	2. W. W.	3. D. C.	4. W. T.	5. A. H.	6. J. W.	8. J. B.	10. Mrs. C.	11. Mrs. D.	12. J. D.	13. Mrs. H.	Average of series.
Height (inches)	65	64	67	71	64.5	68	65	60	61	63	64	
Weight (lb.)	131	?	161	178	119.0	151	137	?	135	114	175	
Age (years)	55	71	64	65	64	48	47	84	72	50	57	
Number of determina- tions of resting rates	10	6	3	4	6	4	5	3	6	6	3	
Resting auricular rates per minute :—												
Maximum	81.8	78.8	78.0	63.1	72.5	57.7	—	—	98.6	91.3	77.3	77.6
Minimum	69.0	69.9	72.0	55.2	58.0	48.4	—	—	84.5	73.1	71.3	66.7
∴ Auricular range =	12.8	8.9	6.0	7.9	14.5	9.3	—	—	14.1	18.2	6.0	10.9
Resting ventricular rates per minute :—												
Maximum	29.2	36.8	42.8	23.6	36.0	28.5	33.0	26.8	51.0	55.2	42.6	36.9
Minimum	21.0	33.8	38.5	22.1	30.6	25.0	29.7	26.5	40.3	46.6	39.8	32.2
∴ Ventricular range =	8.2	3.0	4.3	1.5	5.4	3.5	3.3	0.3	10.7	8.6	2.8	4.7

To show the maximum and minimum auricular and ventricular rates per minute observed in a series of determinations in eleven cases of complete heart-block under conditions of bodily rest. The average auricular and ventricular ranges (i.e. maximum rate less minimum rate) are respectively 10.9 and 4.7. If the ranges be expressed as a percentage of the minimum rates then it becomes apparent that each is of the same order of magnitude (15.1 per cent. and 14.7 per cent.) on the average.

familiar with the laboratory, and during his stay quiet was maintained and strangers excluded. A fall in blood-pressure to uniform readings was taken to indicate that an approximately steady level of nervous and metabolic activity had been reached. Three electrocardiograms were then recorded unknown to the patient. This procedure was repeated with each individual on several occasions at intervals of a few days. The auricular and ventricular rates were calculated from the electrocardiograms and averaged for each attendance of the individual. The results in fifty-six determinations of the auricular and ventricular rates in eleven cases of complete heart-block under fairly uniform conditions are collected in Table I.

A brief study of the rates on different days, but under similar conditions, is sufficient to show that the ventricular rate is not constant even in the same individual. For example, in Case 1, the average of separate determination on ten different days was 24.9, with a maximum of 29.2 and a minimum of 21.0, yielding an available ventricular range under resting conditions of 8.2 beats per minute. Under similar conditions, the auricular range is 12.8 with an average reading of 74.9 contractions per minute. Of the whole series of eleven cases, studied as far as possible under similar conditions, the maximum ventricular rate recorded was 55.2 (Case 12) and the minimum 21.0 (Case 1). The maximum ventricular range at rest was 10.7 (Case 11-6 determination) and the minimum 0.3 (Case 10-3 determination). The ventricular rate under approximately uniform conditions of bodily rest is not a fixed quantity. It varies from day to day, and also, even more considerably in different individuals.

It may therefore be concluded that the ventricular rate in complete heart-block is not a fixed quantity, even under uniform conditions of bodily rest. It tends to fluctuate through a small range more or less peculiar to the individual. In certain subjects the ventricles display a greater percentage range of activity than do the auricles under similar circumstances.

#### *The Relation between Ventricular and Auricular Rates in Complete Heart-block*

It is probable under uniform conditions that the observed rates for auricles and ventricles may bear some definite proportion the one to the other.

Excluding two individuals in whom auricular fibrillation accompanied complete block, forty-nine observations of corresponding auricular and ventricular rates in nine individuals were recorded. Applying the law of least squares, where  $y$  = the ventricular rate and  $x$  = the auricular rate, then from the straight line formula,  $y = bx + a$  there is obtained the regression line  $v - v$  as entered in Fig 1. From this line it is possible to read off a theoretical ventricular rate for a given auricular. Applying the test of correlation it is found that the relation between the auricular and ventricular rates is of fairly high degree. The calculated coefficient of correlation between the

auricular and ventricular rates is  $+0.64$  (perfect positive agreement is  $+1.00$  and absence of correlation is zero). It is therefore established that, not only are the fluctuations in rate of auricles and ventricles of a similar order, but that under resting conditions the actual rates throughout a series of cases are closely related.

On purely clinical grounds it was found possible to classify these cases of complete heart-block into two broad etiological groups—a degenerative and a 'toxic' or unknown variety. The degenerative group was composed of older individuals, presenting evidence of arteriosclerotic changes, and the block occurred apparently as a manifestation of a more or less generalized cardiac fibrosis. Each group had certain features in common, the 'toxic' being composed of a variety of cases of a mixed type, some of whom gave a

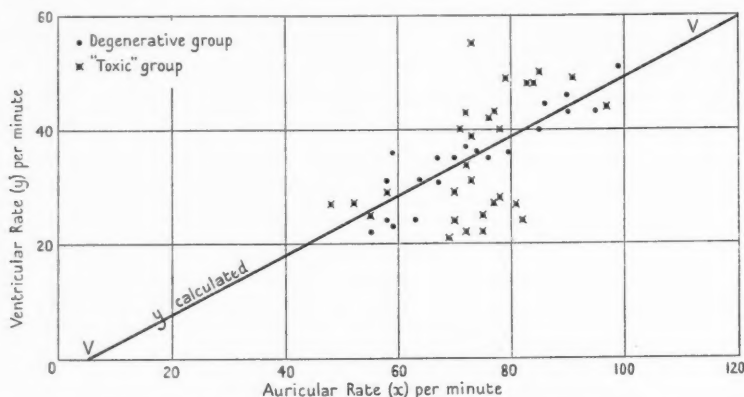


FIG. 1. To show the relation between the auricular and ventricular rates, recorded synchronously in nine cases of complete heart-block under conditions of bodily rest. Forty-nine observations are plotted, and from these the regression line  $v-v$  has been calculated. It will be noted that the points obtained from the 'toxic' group show a greater degree of dispersion than those of the degenerative cases whose rates fall in greater proximity to the regression line.

history of severe infection such as acute rheumatism or diphtheria before the onset of block. Their average age was 55 years, in contrast to the degenerative group in whom age 70 was reached before complete block was diagnosed. When the auricular and ventricular rates were plotted for the whole series of cases, as has been done in Fig. 1, the wide 'scatter' of the points suggested that probably by replotting separately the two groups—degenerative and 'toxic'—a more perfect correlation between auricular and ventricular rates might be demonstrated for one or other. Of the five degenerative cases the rates observed in Cases 2, 4, 5, and 11 are suitable for analysis. Case 10 must be excluded on account of auricular fibrillation.

In Fig. 1 the observed auricular and corresponding ventricular rates of the four degenerative cases are indicated. Mathematical analysis demonstrates a very high degree of correlation in this group of individuals, the coefficient of correlation being  $+0.90$ . In the same figure are inserted the readings obtained

from the five individuals (Cases 1, 3, 6, 12, and 13) included on clinical grounds in the 'toxic' or unknown group. A glance at the plottings is sufficient to demonstrate a sharp contrast when this group is compared with that of the degenerative group. The 'scatter' is over a great range and the regression line is somewhat isolated from the surrounding readings. In the degenerative group the 'scatter' is less, and the plotted points are more compact and more closely associated with the regression line. In other words, the degree of dispersion is greater in the 'toxic' than in the degenerative group. Further, the coefficient of correlation,  $+0.50$  is less perfect in the 'toxic' than in the degenerative group.

The mathematical analysis of the available data demonstrates a fair degree of correlation between the auricular and ventricular rates for all the cases in this series. Moreover, this treatment justifies the proposed clinical subdivision of the cases into two broad groups. The degree of correlation between the auricular and ventricular in the 'toxic' group—composed of a variety of somewhat dissimilar cases—is less perfect than in the elderly arteriosclerotic group. The relatively wide degree of dispersion in the 'toxic' group indicates a more labile regulation of rhythm. Taking the series as a whole, it is evident from the lie of the regression line (Fig. 1) that, under conditions of bodily rest, the optimum ventricular rate in complete heart-block is rather less than half a given auricular rate.

#### *The Response to Exercise.*

Hering's (22) researches led him to the conclusion that the acceleration of the normal heart in response to exertion was due partly to release from vagal inhibition and partly to increased sympathetic stimulation. From the experiments of Favill and White (11) on an individual who was able to produce a voluntary acceleration of the heart it would seem quite definitely established that in man, as in most animals, the normal fluctuations in pulse rate are produced by the combined action of the parasympathetic and sympathetic nerves.

While clinicians (8, 24, 28, 35) have been guarded in attributing to exercise the power of increasing the ventricular rate, yet Erlanger and Blackman (10) demonstrated quite conclusively that in dogs, surviving by several months the operative destruction of the bundle of His, exercise produced a decided increase in the ventricular rate. In three observations the rates before exercise were 49.5, 54.0, and 46.5, whereas after the animals had run about, the respective rates were 55.5, 57.0, and 62.2 beats per minute. A number of authors (2, 13, 25, 26) have reported an increase in the idio-ventricular rate in individual patients under their observation. Occasionally an acceleration has been made good by the addition of extrasystolic beats (36) but the observations of Lian (25), Frédéricq (13), and particularly those of Liljestrand and Zander (26), indicate that the idio-ventricular rate may respond to the demands of exercise as readily and as abruptly as in the normal heart.

Tested with varying amounts of exercise on three occasions the latter authors found in one patient a rise in ventricular rate from 52 to 109, from 52 to 76, and from 41 to 69.

The literature contains records of only half a dozen cases of complete heart-block complicated by pregnancy and spontaneous delivery. It is of interest to note that in Dressler's (9) case the ventricular rate increased during the muscular straining of labour from 36 to 52 beats per minute. Titus and Stevens (34) made careful observations on a similar case. Shortly before the onset of labour the auricular and ventricular rates were 68 and 45. During the muscular efforts of delivery they rose to 88 and 72 respectively. After the birth of the child the rates were 57 and 38.

It would therefore appear that an inability to accelerate the ventricles is not an essential feature of complete heart-block. This conclusion is supported by the results obtained in the eleven cases which comprise the present study. In three patients a modified test was used, cases 2 and 11 being confined to bed on account of peripheral congestion. Case 10 was a feeble old woman unable to perform the routine test which was used by the remaining patients. The results obtained after a standard exercise test in eight individuals (Cases 1, 3, 4, 5, 6, 8, 12, and 13) may therefore be considered suitable for comparison.

After the patient had rested on a couch for about 20 minutes until the blood-pressure and pulse-rate had assumed fairly steady levels, a strip of electrocardiographic film was exposed, generally by Lead I. The electrodes, which consisted of jars of saline into which the hands were immersed, were found to be particularly convenient, as on the completion of exercise the patient had simply to return to the couch, lie down and place the hands in the saline solution. In this way the time elapsing between the end of exercise and the first electrocardiogram was reduced to a minimum. By having the film already running, and the deflection of the fibre previously standardized, it was possible to secure accurate records of the heart's rate within 5 seconds of completing the test. The technique outlined above permitted records to be obtained with the minimum amount of delay. As a general rule the film was allowed to run until 30 seconds had elapsed from the time of completing the test. Thereafter, further records were made at alternate 15 second intervals for  $1\frac{1}{2}$  minutes or for such additional periods as seemed desirable. The test of physical activity consisted in ascending and descending two steps a variable number of times in a given period. The apparatus, which was made for the purpose, consists of a two-step contrivance, the patient climbing up two steps on one side and down two steps on the other. Each step is exactly 9 inches high (and about 22 inches wide). The patients were instructed to climb over the steps and back again, as quickly as possible, in the space of  $1\frac{1}{2}$  minutes. By making the total height of the two steps  $1\frac{1}{2}$  feet, and by limiting the exercise period to  $1\frac{1}{2}$  minutes, the calculation of the amount of work done per minute is greatly simplified. This plan, whereby the amount of work done can be compared with the

pulse-rate changes, forms the basis of the test of circulatory efficiency devised by Master and Oppenheimer (30). It has the great advantage that the method is both simple and convenient in its execution, and provides a ready means of regulating the amount of work done in a given time. The patients co-operated to the best of their ability, and in each instance sufficient physical exertion was undertaken to induce definite dyspnoea, and even in certain instances some degree of orthopnoea. Two patients suffered from praecordial pain immediately after the test (Cases No. 3 and 8).

*The Changes in Auricular and Ventricular Rates due to Physical Exertion.*

From the long strips of film recorded immediately after exercise, the auricular and ventricular rates have been calculated and compared with the

TABLE II

Case No. and initials.	Auricular rate.			Ventricular rate.			Rate of work done. Foot-pounds per minute.
	Before exercise.	After exercise.	Gain in rate.	Before exercise.	After exercise.	Gain in rate.	
1. Mrs. T. (a)	72.1	129.6	57.5	22.0	33.0	11.0	? 2,500
(b)*	89.6	144.0	54.4	30.3	38.1	7.8	2,700
3. D. C.	102.0	128.7	26.7	43.6	57.4	13.8	3,519
4. W. T.	50.6	97.4	46.8	43.2	46.2	3.0	3,249
5. A. H. (a)	67.3	116.3	49.0	34.8	36.0	1.2	2,950
(b)	66.3	111.3	45.0	30.7	35.4	4.7	2,236
6. J. W.	55.6	131.0	75.4	25.2	32.6	7.4	3,021
8. J. B.	Auricular fibrillation			35.3	43.2	7.9	2,346
12. J. D. (a)	73.1	88.3	15.2	55.2	68.6	13.4	2,052
(b)	79.2	123.8	44.6	48.7	82.9	34.2	2,790
13. Mrs. H.	71.1	110.0	38.9	39.8	90.0	50.2	2,975

To show the effect of exercise on the auricular and ventricular rates in eight patients able to take part in a standard exercise test. In each instance a quickening of the ventricular rate was induced.

\* Taking ephedrine by mouth at this time.

time elapsing from the commencement of the recovery period. The results obtained in eleven exercise tests in eight patients are presented in Table II. By comparing the rates before exercise with those observed within twenty seconds of completing the test it is evident that in every instance physical exertion produced an increased rate of ventricular beating. The minimum gain in rate was 1.2 beats per minute (Case 5) and the maximum 50.2 beats (Case 13). That an adequate amount of exertion was undertaken in each experiment is evident from the calculation of the work done by the different individuals. Of the eight patients studied by this means Table II shows that in two individuals (Cases 4 and 5) the degree of ventricular acceleration was considerably less than in the others of the series. Both these men belonged to the degenerative group in which the available clinical evidence suggested that the lesion causing the block was primarily of vascular origin. The available facts from which to draw conclusions are scanty, but it may be that the response of the blocked heart to

exertion is influenced in some measure by the age of the patient, the presence of diffuse coronary artery disease and the nature of the lesion responsible for the production of the dissociation. It is noteworthy that in the other cases the ventricles accelerated more freely to similar amounts of bodily exertion.

Reference has already been made to three subjects (Cases 2, 10, and 11) who were of such feeble constitution as to prevent them undertaking the more formal exercise test. All were arteriosclerotic subjects, over 70 years

TABLE III

Case No. and initials.	Auricular rate.			Ventricular rate.			Remarks.
	Before exercise.	After exercise.	Gain in rate.	Before exercise.	After exercise.	Gain in rate.	
2. W. W. (a)	69.9	88.4	18.5	34.8	35.1	0.3	Sat up and down 6 times
(b)	71.5	83.5	12.0	33.8	34.9	1.1	Sat up and down 6 times
10. Mrs. C.	Auricular fibrillation			26.8	27.3	0.5	Walked 10 yds.
11. Mrs. D.	84.5	111.1	26.6	40.3	40.4	0.1	Walked 10 yds.

To show the effect of a modified exercise test in three individuals unable to perform the standard test. In functional efficiency all belonged to Group 3.

of age, and all have since died. In each instance a modified test was performed. In Case 2 the effect of bending the trunk backwards and forwards at the hips about half a dozen times was as much as could be accomplished. Case 10 was a frail old woman 84 years of age, and in this instance the effect on the heart-rate of walking slowly across the room was recorded. In Case 11 the test was restricted to walking a distance of ten yards. Table III records the effect of a modified test in these three individuals who by age and infirmity were unable to engage in the standard test. While definite auricular quickening was induced in each instance, the ventricles increased in rate but slightly.

#### *The Course of the Reaction to Exertion*

The rate of the recovery process after a short burst of exercise is best presented diagrammatically. Two experiments may be selected as representative of the short duration of the effect on the rate of the ventricles. The electrocardiograms recorded in Case 1 show initial auricular and ventricular rates of 89.6 and 30.3 per minute. After  $1\frac{1}{2}$  minutes exertion the rates were 144.0 and 38.1. Within  $1\frac{1}{4}$  minutes of completing the test the ventricular rate returned to the pre-existing level. Extrasystoles were not observed in this patient.

Case 13 showed an exceptional reaction to exercise. Seven seconds after completing the test the ventricular rate (as shown in Fig. 3) reached 90 per minute. The corresponding auricular rate is difficult to calculate accurately from the electrocardiogram but is in the neighbourhood of

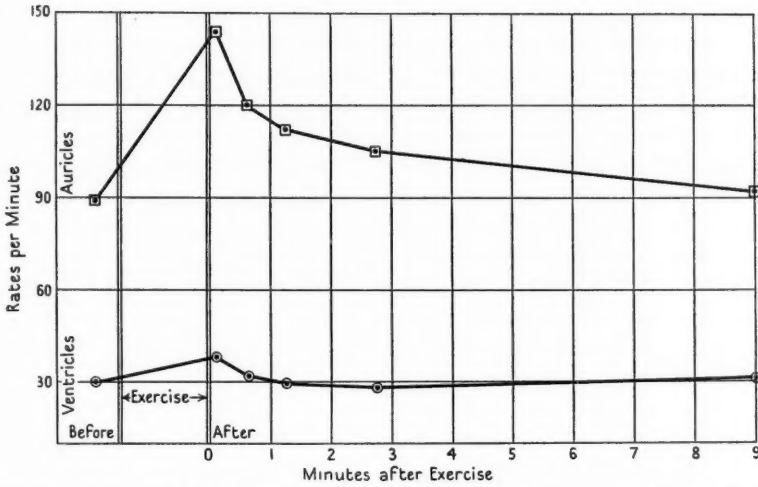


FIG. 2. To show the auricular and ventricular rates before and after  $1\frac{1}{2}$  minutes exercise in Case 1. The ventricular rate increased from 30.3 to 38.1 beats per minute.

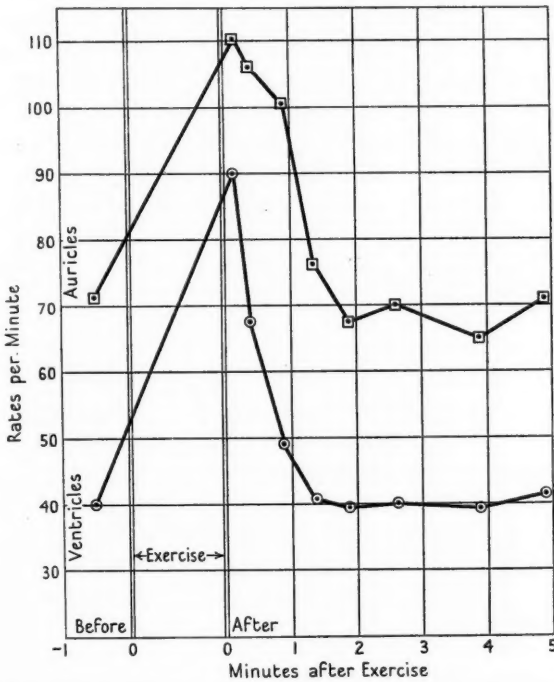


FIG. 3. To show the remarkable effect of exercise in Case 13. Despite the persistence of complete block the ventricular rate increases from 39.8 to 90.0 per minute.

110 per minute. Recovery is rapid. Within  $1\frac{1}{2}$  minutes auricles and ventricles approximate to their resting values (Plate 20).

It would therefore appear that the assumption that the ventricular rate is a fixed and stable quantity and uninfluenced by exertion is incorrect. The power of the blocked heart to increase its rate under a more or less uniform degree of stimulation varies considerably in different individuals. Similarly, the rate of the recovery process (after a short burst of strenuous exercise) also varies in different individuals. In some the ventricles return to their pre-existing rate within a minute of completing the test; in others three, four, or five minutes may elapse before the rates became re-adjusted to resting conditions.

#### *The Maximum Range in Ventricular Rate*

It has already been shown that under uniform conditions of bodily rest fluctuations in the rates of auricles and ventricles occur from day to day in the same subject, and when the extent of the variations (i.e. the range in rate) in auricles and ventricles is compared it is found that for each the magnitude of the range is much of the same order. In an attempt to assess the power of the idio-ventricular centre to vary its rate, it is proposed to study the extremes of rate, the maximum induced by muscular exertion on the one hand and the minimum rate observed during prolonged physical inactivity on the other.

For our present purposes the maximum natural range in rate may be defined as the difference between the rate immediately after a more or less standard exercise test and the minimum rate of a series of observations during states of prolonged bodily inactivity. Such a standard may be conveniently applied to a number of individuals, though it is permissible to point out that the maximum and minimum rates thus recorded are not absolute points for reckoning the range. For instance, in certain individuals it was possible to induce a faster ventricular rate during the course of the febrile reaction to a foreign protein. Similarly the slowest rate observed during a prolonged rest is not necessarily the absolute minimum rate for the individual. Slower rates may have passed undetected. Actually, in certain instances, the rate of the ventricles after full digitalization (19) or during sleep was a few beats less per minute than that observed to occur spontaneously. These extremes, produced by the presence of fever or after thorough digitalization are not of immediate concern.

Under the conditions described above it is found that the maximum natural range of rate for auricles and ventricles varies considerably in different individuals. The findings are presented in the accompanying Table (No. IV) in which the minimum rates are contrasted with the maximum rates for seven individuals (1, 3, 4, 5, 6, 12, and 13) all of whom were sufficiently active to indulge in a standard exercise test. Four cases are excluded, Nos. 8 and 10 on account of auricular fibrillation, and Nos. 2

and 11 on account of general muscular weakness. In the seven individuals exercise produced a notable increase in the ventricular and auricular rates. Averaging this series it is found that the *a-v* ratio under resting conditions is 64.3-31.9, and after exercise 119.5-54.0, the respective ranges being 55.2 and 22.1. The two latter figures represent a percentage increase over the minimum resting rates of 89.6 and 66.7 respectively for auricles and ventricles.

TABLE IV

Case No. and initials.	Minimum resting rates.		Maximum rates after exercise test.		Maximum range in rate.			
	Auricles.	Ventricles.	Auricles.	Ventricles.	Auricular.		Ventricular.	
					Actual range.	As % of min. rate.	Actual range.	As % of min. rate.
1. Mrs. T.	69.0	21.0	129.6	33.0	60.6	87.8	12.0	57.1
3. D. C.	72.0	38.5	128.7	57.4	56.7	78.8	18.9	49.1
4. W. T.	55.2	22.1	97.4	46.2	42.2	76.5	24.1	109.0
5. A. H.	58.0	30.6	116.3	36.0	58.3	100.5	5.4	17.6
6. J. W.	51.5	25.0	131.0	32.6	79.5	158.5	7.6	30.4
12. J. D.	73.1	46.6	123.8	82.9	50.7	69.4	36.3	77.9
13. Mrs. H.	71.3	39.8	110.0	90.0	38.7	54.2	50.2	126.1
Average of series.	64.3	31.9	119.5	54.0	55.2	89.6	22.1	66.7

To show the maximum natural range in the rate of auricles and ventricles in seven cases of complete heart-block. The range in rate is estimated by taking the difference between the rate after a standard exercise test and the minimum rate of a series recorded after a prolonged rest on a couch.

The accompanying graph (Fig. 4) demonstrates that the auricular and ventricular ranges are not of the same order of magnitude. Were they similar then the points in the graph would fall along a line extending from the bottom left hand corner to the top right hand—almost exactly the opposite to that observed. It becomes evident from the lie of the plottings—admittedly few in number—that the general tendency points to an inverse relationship between the auricular and ventricular ranges.

The regression line (V-V) entered on the Chart (Fig. 4) represents the percentage ventricular range (*y*) for a given auricular (*x*). From this it is evident that in this small series of cases an increase of approximately 150 per cent. in auricular rate is accompanied by only 10 per cent. in ventricular; whereas a 50 per cent. gain in auricular rate coexists with a 100 per cent. gain in ventricular. In other words, under a standard test of the maximum range it is found that the greatest auricular acceleration occurs in association with a minimal ventricular gain in rate. The observations are admittedly too few to treat mathematically or to analyse in detail, but it is not without interest to speculate on the mechanism regulating the peculiar relationship which appears to exist between the auricular and ventricular ranges.

*The Inverse Relation between the Auricular and Ventricular Ranges*

Exercise increases the frequency of the normal heart in virtue of a number of circulatory reactions amongst which the principal factor concerned is the Bainbridge reflex (4). As a result of increased venous pressure afferent impulses are transmitted along the vagus from its nerve endings in the right auricle and great veins, producing a reflex depression of the vagal centre, and to a less extent a stimulation of the sympathetic acceleration

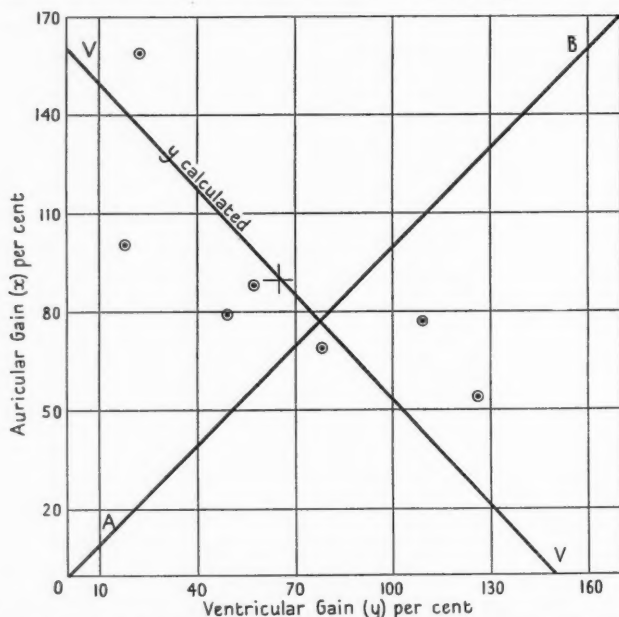


FIG. 4. To show that the maximum auricular and ventricular ranges are not of the same order of magnitude. Were they similar the points would tend to fall along the line *A-B*, instead of which their lie is more or less at right angles to the line *A-B* as indicated by the regression line *V-V*. This points to an inverse relationship between the maximum auricular and ventricular ranges.

fibres with the result that the frequency of the heart beat is augmented. It is of interest to note that the degree of cardiac acceleration is proportionate to the rise in venous pressure (37). The venous return is greatly increased by even a short bout of exercise. The increased respiratory movements, the contractions of the skeletal muscles, and the associated rise of capillary pressure are the chief factors responsible for the augmented venous flow to the right auricle. By means of the Bainbridge reflex the rate of the heart is therefore adopted to the venous return.

In complete heart-block the ventricles are dissociated from the normal pacemaker of the heart. It is reasonable to suppose that, if the ventricles be incapable of an adequate readjustment to an increased venous return, then auricular distension with further augmentation of the Bainbridge reflex must occur. A slight increase in ventricular rate may be partly com-

pensated by a greater volume output per beat, but should the venous supply exceed the demand, then excessive auricular acceleration is all the more likely. On the other hand, in those instances where the ventricles respond by a brisk increase in rate (and probably also in stroke volume) venous distension of the auricle must be of minor degree. Hence the range in auricular rate is likely to be less where the ventricle is better adapted to the demands of exercise. This suggestion finds support from the clinical observations that the individuals with the greatest percentage increase in auricular rate (and the least ventricular gain) were decidedly more dyspnoeic after the exercise test than those in whom the ventricular increase was maximum and the auricular least.

It would therefore appear that the less successful the ventricles are in adapting themselves to the demands of muscular exercise the more does the auricle accelerate in an endeavour to overcome the venous distension. This does not imply that the auricular beat has necessarily any decided influence on ventricular filling, although Read (31) quotes Gesell (16) in support of her contention that in man, in the presence of complete heart-block, the auricular contractions do play a part in filling the ventricle. Gesell came to the conclusion that auricular systole increased the ventricular output by 50 per cent. over that maintained by venous pressure. It is, however, probable that as a result of the Bainbridge reflex, every endeavour is made to compensate for auricular engorgement.

#### *Myocardial Efficiency in Relation to the Maximum Range in Ventricular Rate*

From the data already presented it is evident that the maximum range in the rate of the ventricles varies very considerably in different individuals. In an attempt to correlate the range with the individual's minimum ventricular rate it is found that one is not a function of the other. Similarly, in this series of cases, but little correlation exists between the age of the subject and the maximum ventricular range, though it might be anticipated that in the younger individual a wider fluctuation in rate would be observed than in those instances where the block was associated with senility.

On the other hand, the available range in rate appears to bear a definite relationship to the individuals' capacity to undertake muscular exertion. Analysis of the available facts reveals that the range in ventricular rate is greatest in those whose symptoms after exertion are the least distressing. An attempt has been made on clinical grounds to grade individuals according to their ability to undertake physical activity, using the method of classification suggested by the American Heart Association (3). Practical experience of this system extending over a number of years has proved its worth, particularly in relation to the assessment of the fitness of cardiac patients for the strain of pregnancy and delivery (20), and there is no reason to suppose that in its application to cases of heart-block the conclusions are any less valid. For purposes of grading patients according to their functional capacity, three broad groups may be considered.

Group 1, consists of patients who are able to carry out all their ordinary physical activities without discomfort. Of the present series Case 13 may be placed in this group. This woman had only slight distress on severe exertion, and the presence of complete heart-block was only detected in the course of a routine examination. Group 2 is composed of patients unable to carry out their ordinary physical activities without discomfort. There are two sub-divisions in this group, (a) consisting of those whose incapacity is slight, and (b) those having a definite limitation of physical activity. Of the present series, Cases 1, 3, 4, and 12 may be selected as suitable for inclusion in Group 2a, and Cases 5, 6, and 8 in Group 2b. Group 3 consists of those patients with symptoms and signs of heart failure when at rest. Unable to perform any additional physical activity without discomfort, their capacity for exertion is greatly limited. Three individuals—Cases 2, 10, and 11—belong to this group.

TABLE V

Case No. and initials.	Maximum range.		Functional efficiency group.	Average ranges for each group.	
	Auricles.	Ventricles.			
13. Mrs. H.	38.0	50.2	1. (No symptoms)	38.0	50.2
1. Mrs. T.	60.6	12.0	2a. (Slight distress)	52.6	22.8
3. D. C.	56.7	18.9			
4. W. T.	42.2	24.1			
12. J. D.	50.7	36.3			
5. A. K.	58.3	5.4	2b. (Definite disability)	68.9	7.5
6. J. W.	79.5	7.6			
8. J. B.	a. fib.	9.5			
2. W. W.	18.5	3.0	3. (Congestive heart failure)	22.6	1.3
10. Mrs. C.	a. fib.	0.8			
11. Mrs. D.	26.6	0.1			

To show that the ventricular range is least in those in whom the cardiac reserve power is minimal. Conversely, the ability to quicken the ventricular rate through a wide range is accompanied by a few or no cardiac symptoms.

In Table V the related facts are conveniently displayed. Comparing the functional groupings it is evident that as myocardial efficiency declines from Group 1 to Group 3, so does the available ventricular range tend to decrease. In the circumstances it seems justifiable to conclude that in a general way the ventricular range varies directly with the individual's capacity to undertake exertion. This implies that in general those sufferers from complete heart-block who are the better able to augment the ventricular rate, when physical exertion is undertaken, suffer the least distress and have a correspondingly high degree of myocardial efficiency.

#### *The Effect of Sleep on the Ventricular Rate in Complete Heart-block*

In the preceding pages it has been pointed out that the minimum rate used in the calculation of the ventricular range was that found to occur under uniform resting conditions during the forenoon with the patient awake.

That such a determination of the heart-rate is probably not the absolute minimum is supported by the fact that, at least in health, slower rates have been observed during sleep than in the basal state. The truth of Galen's (14) dictum '*pulsus in somno parvi, languidi rari*' has been confirmed and elaborated many times, notably by Boas and Goldschmidt (5), in recent years. Similarly Sutherland and McMichael (33) found amongst thirty convalescent children that the average sleeping rate was 73, whereas the average rate awake was 107—a difference of 34 beats per minute.

In the three cases of complete heart-block in which attention was directed to the influence of sleep on the idio-ventricular rate the pulse was counted for two consecutive minutes by a nurse in attendance during the early morning hours, while the patient slept. A note was made at the time at which the sleeping rate was observed, and twelve hours later, a second count was made, the patient having remained in bed and being awake. In this way it has been possible to contrast sleeping and waking rates employing a uniform method of observation. An attempt was made to record the sleeping rate on a series of consecutive days—but this was not always possible as the patient's hours of sleep sometimes varied considerably. The depth or duration of sleep at the time of counting was not measured.

TABLE VI

Case No. and initials.	Average rates counted by hand.		No. and hour of determinations.	Difference between awake and asleep rates.	Minimum resting rates (from e. c. g's) as in Table I.	Difference between min. resting rate and sleep rate.
	Asleep.	Awake.				
10. Mrs. C.	22.4	23.1	10. (2 a.m. & 2 p.m.)	0.7	26.5	4.1
12. J. D.	45.6	56.0	6. (11 p.m. & 11 a.m.)	10.4	46.6	1.0
13. Mrs. H.	39.0	45.6	6. (4 a.m. & 4 p.m.)	6.6	39.8	0.8

To show that in three patients confined to bed, the heart-rate was less during sleep than during waking hours.

From Table VI it is evident that for these three individuals the sleeping ventricular rate was 4.1, 1.0, and 0.8 beats per minute less than the minimum resting rate recorded during the forenoon by the electro-cardiograph. The difference may well be greater than these figures indicate, for it is known that the heart-rate fluctuates during sleep, and that absolute minimum rate occurs at different times, not only in different healthy subjects, but even in the same individual. For this reason the rates recorded in these three patients during their natural sleep do not necessarily represent the absolute minimum sleeping rate. The figures merely express counts made at a given time during sleep. The studies of Klewitz (23) and of Boas and Goldschmidt (5) have demonstrated that during sleep the customary fall in heart-rate does not occur in the presence of myocardial insufficiency. The probability is that a similar conclusion holds good in cases of complete

heart-block—a reduced range of ventricular rate during sleep being associated with a much impaired response to effort.

*The Effect of Fever on the Idio-ventricular Rate*

The literature contains little or no information regarding the precise effect of a rise of temperature on the idio-ventricular rate in man. Schwartz (32), for instance, states 'It would seem probable that in complete heart-block due to organic involvement of the bundle of His, the factor of pyrexia may be discounted as responsible for increasing the ventricular rate'. As will be shown immediately, the facts at my disposal are at variance with this conclusion.

It was observed that on those occasions on which certain patients had a trifling spontaneous rise of temperature to 98.6, or thereabout, that the ventricular rate appeared to quicken by one or two beats. The opportunities for making more precise observations being scanty, it was decided to test the effect of an artificially-induced pyrexia on the ventricular rate.

After an ample control period of ten or fourteen days, during which hourly or two-hourly pulse-rates and mouth temperatures were recorded, and electrocardiograms registered daily, a 'protein-shock' reaction was induced in three patients (Cases 1, 5, and 13). Each patient received a 30 million dose of a stock *B. typhosus* vaccine intravenously. Thereafter, pulse-rate and temperature were accurately recorded at hourly intervals throughout the pyrexial period. It is a common experience that the 'incubation' period elapsing between the administration of the vaccine and the onset of pyrexia varies considerably in different individuals. For this reason it was not always possible to record electrocardiograms during the height of the reaction, but nevertheless by registering the heart-beat in association with the temperature reaction observed during the day hours, it was possible to check the pulse counts and derive information regarding the auricular rate. The essential details of three experiments are recorded in Table VII.

TABLE VII

Case No. and initials.	Increase in temperature.	Ventricular rate.			Gain in rate per 1° F.
		Before inoculation.	Maximum during fever.	Gain in rate.	
1. Mrs. T.	6.8°	26.0	45.0	19.0	3.58
5. A. H.	5.2°	29.2	48.0	18.8	3.63
13. Mrs. H.	4.8°	43.5	64.0	20.5	4.27

∴ Average rise in ventricular rate for an increase of 1° F. = 3.82 beats per minute.

To show the average gain in ventricular rate for a rise of temperature through 1° F.

These figures demonstrate that the ventricles of the blocked heart respond in rate to a rise of temperature. Lyon (27) has shown that, in the presence of normal sinus rhythm an increase of 1° F. causes a rise in the pulse-rate of 9.13 beats per minute. The figures at our disposal are too few to submit to precise methods of mathematical analysis.

From the limited material available, the results suggest that in contrast to the healthy heart a rise of  $1^{\circ}\text{F.}$  is associated with an increase in the ventricular rate of about four beats per minute. If it be assumed that under resting conditions the sino-auricular node has a natural frequency of 70 per minute and that a rise of  $1^{\circ}\text{F.}$  produces an increase of 9.13 beats, then as a matter of simple proportion the ventricles, with a spontaneous frequency of, say, 30 ought to augment their rate by 3.91 beats per minute for a similar elevation of temperature. This is in close agreement with the average value of 3.82, shown in Table VII. It would, however, be desirable to submit a large number of corresponding rates and temperatures to exact methods of analysis. The course of the protein shock reaction in Case 5 is depicted in Fig 5.

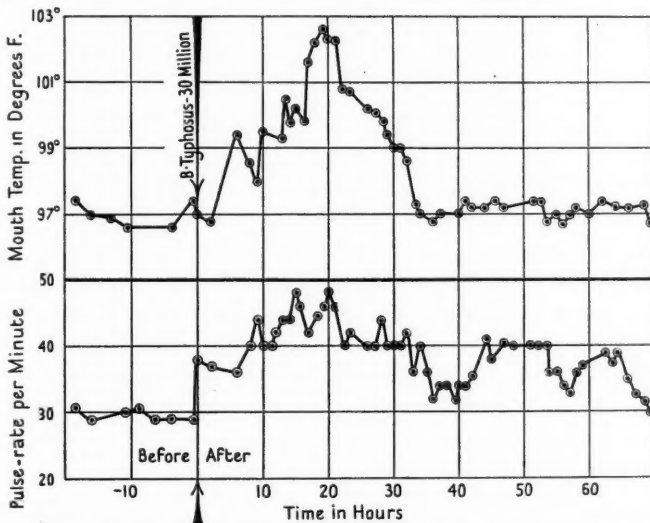


FIG. 5. To show the course of the febrile reaction to the intravenous injection of a 30 million dose of a *B. typhosus* vaccine in Case 5.

It is well known that changes in temperature have a profound effect on the functional activity of certain tissues. Gaskell (15) showed that by applying heat to the frog's sinus a marked increase in the rate of the heart resulted. Similar observations were made on the influence of temperature on the activity of the sino-auricular node in the mammalian heart by McWilliam (29), Adam (1), and Flack (12). Moreover, Zahn (38) has shown that rhythms arising in the auriculo-ventricular node are accelerated by heating and retarded by cooling the region of the node itself. Brunton (6) and Clark (7) have concluded that vagal activity is diminished by heat.

From the facts derived from the 'protein shock' reaction in three patients suffering from complete heart-block, and from the results of temperature experiments on the isolated heart, it seems reasonable to conclude that the idio-ventricular rhythm is highly susceptible to changes in body temperature.

In fact, a sufficient rise of temperature may be accompanied by a greater elevation of the ventricular rate than that induced by the most severe physical exertion which the individual is capable of undertaking. Broadly speaking, in complete heart-block a rise of  $1^{\circ}\text{F.}$  may account for an increase of about four beats per minute.

#### *Summary and Conclusions*

The ventricular rate in complete heart-block is not fixed, but under conditions of bodily rest fluctuates through a range of rate more or less peculiar to the individual.

Clinically it was possible to divide these cases into broad groups—a degenerative, and a 'toxic' variety. The coefficient of correlation between the auricular and the ventricular rates is less perfect in the 'toxic' than in the degenerative group, indicating a more labile regulation of the independent rhythms in the former.

Muscular exercise increases the rate of ventricular beating in complete heart-block. A simple test, consisting of repeatedly climbing a height of  $1\frac{1}{2}$  feet in a given time, induced a maximum increase of 50.2 beats per minute in one patient, and a minimum of 1.2 beats in another.

The power to increase the rate of ventricular beating in response to exertion varies considerably in different individuals. Similarly the rate of the recovery process is inconstant. In some patients the ventricles return to their pre-existing rate within one minute of completing the test; in others three, four, or five minutes may elapse before the rates become fully readjusted to resting conditions.

The maximum natural range in auricular and ventricular rates has been estimated by taking the difference between the rate recorded immediately after exercise and the minimum rate observed in a series of observations for each individual under conditions of prolonged bodily rest. The maximum range in rate varies in different subjects, and the maximum auricular and ventricular ranges are not of the same order of magnitude.

In this series of cases it is found that the maximum auricular and ventricular ranges vary inversely. A range of 150 per cent. in auricular rate is accompanied by only 10 per cent. in ventricular; a 50 per cent. gain in auricular rate coexists with a 100 per cent. gain in ventricular. In other words, the greater the limitation in ventricular range the more labile the auricular.

The greater the ventricular range the less incapacitating are the cardiac symptoms. In complete heart-block an important factor in promoting myocardial efficiency is the ability to quicken the ventricular rate in response to the demands of physical exertion.

In three patients it was found that during sleep the ventricular rate was slower than that recorded under similar conditions awake.

Fever increases the rate of ventricular beating in complete heart-block.

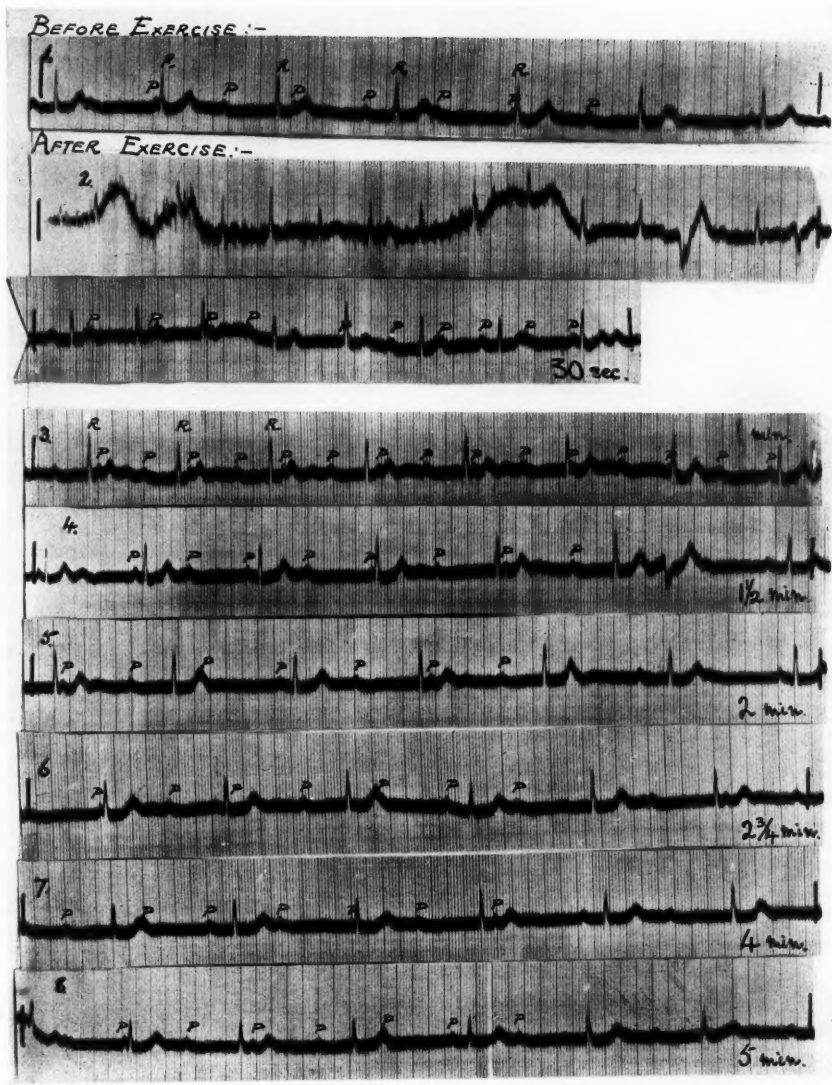
In the course of the 'protein-shock' reaction a rise of  $1^{\circ}$  F. may account for an increase of about four beats per minute in the rate of the ventricles.

These observations suggest that functionally there is no essential difference between the sino-auricular node and the idio-ventricular centre. Each reacts to similar forms of stimulation, but the magnitude of the responses would appear to be limited chiefly by the natural differences in rhythmicity of the two centres of impulse production.

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Sections from successive electrocardiograms recorded before and after the exercise test in Case 13. The auricular and ventricular rates are charted in Fig. 3. Reduced  $\frac{3}{1}$



MASSIVE ATELECTATIC BRONCHIECTASIS<sup>1</sup>

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With Plates 21 to 24

ATELECTASIS of an entire lobe (lobar atelectasis) occurring in bronchiectasis has become a clinical entity (1). Many of the conclusions arrived at by the study of lobar atelectasis are substantiated by the present report which deals with cases of bronchiectasis involving one entire lung (massive atelectasis). The peculiar clinical picture of these cases of so-called massive atelectatic bronchiectasis has led to the suggestion that at least some are congenital in origin.

In 1885 Heller (2) published the first pathological description of atelectatic bronchiectasis. At post-mortem examinations he found that the area with dilated bronchi was surrounded by tissue free from pigment, which suggested to him that that part of the lung had never functioned. Heller believed that there was absence of inflation of the alveoli after birth and that the bronchi became dilated owing to the pull of the enlarging thoracic cage and to the pressure of the accumulating secretions in the bronchi. Herxheimer (3) reported these pigmentless bronchiectatic areas occurring as part of a lobe, as an entire lobe, or a whole lung. Hueter (4) attacked the hypothesis that these areas represented alveoli which had failed to expand because there was such a small amount of alveolar elastic tissue found, which he thought would not disappear if once present. He, therefore, argued that the alveoli had never developed and the condition was a congenital developmental defect. Edens (5), however, claimed that alveolar elastic tissue in the bronchiectatic area may actually be destroyed until none is recognizable. It is evident that there is some doubt as to the importance of the absence of alveolar elastic tissue as an indication of whether or not alveoli have ever been present. There is a third possibility that the alveoli were inflated and functioned normally and then became deflated or atelectatic.

This possibility has arisen since Garnier (6) showed that even the pigment test to ascertain whether the parenchyma has functioned or not is of little value. He claimed that pigment may be present in a lung which has never had alveoli, or in which the alveoli have never expanded, because it may be absorbed from the bronchi. He also showed that pigment may be removed

<sup>1</sup> Received March 14, 1934.

by the lymphatics from an atelectatic bronchiectatic lung which had formerly been a functioning lung. Ziegler (7) stated that the result on the bronchi was the same whether the alveoli had failed to develop or had developed but failed to inflate at birth, or had become inflated and later deflated.

Of the three possibilities the only true congenital atelectatic bronchiectasis is where the alveoli have failed to develop, and it is so far impossible by pathological examination to determine this fact. The difficulty in recognizing congenital bronchiectasis of any type by pathological examination is emphasized by Henke and Lubarsch (8) who state that it is extremely difficult to be sure that bronchiectasis is congenital unless it is found in a foetus or new-born baby. Despite this difficulty, cases of bronchiectasis are frequently diagnosed as congenital in origin. Sauerbruch (9) believes that many cases of bronchiectasis in adult life are congenital in origin, because in many patients symptoms start in childhood. He neglects the fact that bronchiectasis often follows infectious disease occurring in the first few years of life, such as whooping-cough. Whether cases of atelectatic bronchiectasis are congenital or not, it seems clear from pathological evidence that congenital bronchiectasis cannot be distinguished from atelectatic bronchiectasis arising later in life since the ultimate effect on the bronchi appears to be the same. Pasteur (23) in 1913 described massive collapse of one or both lungs which he attributed to deficient respiratory power.

Not only is it extremely difficult to make a pathological diagnosis, but it is even more difficult to make a clinical diagnosis of any type of congenital bronchiectasis with certainty. In any patient more than a few weeks of age a clinical diagnosis of congenital bronchiectasis should be made with a great deal of hesitation. However, in the following case, we believe that a provisional diagnosis of congenital atelectatic bronchiectasis of the left lung is justified.

*Case 1.* Miss E. B., aged 36, was referred to me with a diagnosis of pulmonary tuberculosis. At the time of consultation, May 1931, the patient had no symptoms apart from a slight cough and sputum and felt perfectly well. In January, 1931, she had contracted a head cold, which was unusual for her, and subsequently a cough developed with slight purulent expectoration. The cough lasted for three weeks, and although she felt perfectly well she was rather concerned regarding its continuance and consulted a physician. The X-ray report stated that tuberculous disease was present on the left side. The patient was advised to go to a sanatorium for the 'cure', including collapse therapy.

At the time of examination the cough was slight with a small amount of sputum; otherwise, she was symptomless. On careful inquiry into previous illnesses it was discovered that she had been a remarkably healthy person, and had never been in bed on account of illness. She had escaped the childhood diseases—whooping-cough and measles—and had had no period of ill health. The patient was a highly intelligent person and these statements regarding childhood diseases were confirmed by her mother.

*Examination.* The patient looked healthy. General examination, apart from the chest, was negative. The left side of her chest was seen to move

less than the right. The trachea and heart appeared to be moved to the left. There were no demonstrable changes in percussion, but on auscultation loud bronchial breath sounds were heard over the entire left side, with bronchophony and showers of coarse crackling râles. The right lung appeared normal. Six specimens of sputum examined for tubercle bacilli were negative. The temperature was normal.

Plain X-ray photographs (Fig. 1a) showed a normal right lung with mediastinum shifted to the left. On the left side there were peculiar whorl-like markings from apex to base. There were no areas of calcification or shadows indicating progressive tuberculous disease.

In view of the history, physical findings, and X-ray appearance a tentative diagnosis of bronchiectasis was made, and it was decided to inject iodized oil into the left lung. This was done and the X-ray photograph (Fig. 1b) showed peculiar widespread bronchial dilatations from apex to base. These cavities appeared very thin-walled, were of various sizes, and curiously shaped.

The patient reported back one month later, at which time she stated that her cough and sputum had completely disappeared. For eight months after she had continued to enjoy excellent health with no symptoms.

In view of the history it was felt that this was probably a case of atelectatic bronchiectasis in which the alveoli were maldeveloped or had failed to inflate at birth. It seems improbable that the parenchyma in the bronchiectatic lung had been inflated and then become atelectatic or fibrosed on account of an infectious process causing bronchial obstruction and subsequent parenchymal inflammation. If this were the case, one would expect some history of previous ill health and later, more evidence of irregular fibrosis or thickening of the lung as shown by clinical and X-ray examination.

Subsequent to the study of Case 1, four patients with very similar plain X-ray photographs have been under observation and, after iodized oil injection, showed the same peculiar dilatations.

The second case gave a history of central bronchial obstruction which had been relieved.

*Case 2.* T. S., aged 34, admitted as a case of pneumonia to the medical wards of the Toronto General Hospital, March 19, 1932. Five days previous to admission to hospital patient began to feel very miserable, chilly, and feverish; his cough increased and sputum was blood-tinged. On inquiry into his previous history we learned from him and from his mother that he had been well until two years of age when he aspirated a plum stone and became ill with high fever and cough—no expectoration. He became emaciated. The doctor informed the mother that the trouble was in the left lung. The illness continued for six months, at which time the patient coughed and vomited up a considerable quantity of pus along with the plum stone. Immediate improvement occurred; the patient gained weight and was very soon symptomless, without cough or sputum. When he was 20 years of age, he had influenza and 'pneumonia' on the left side. He was ill for some weeks, and ever since has had cough with chunky yellow sputum, moderate in amount, never foul smelling, and not containing blood.

*Physical examination.* The patient was very ill, with high fever (105°); respiration 45; pulse 120; white-blood count 29,000; clubbing of fingers. Chest: mediastinum markedly shifted to left: impaired resonance; bronchial

breath sounds; showers of fine and medium crackling râles and sibilant rhonchi over entire left lung. There were also a few fine râles at right base posteriorly. He was very ill for two weeks, then his temperature came to normal and he improved noticeably; sputum continued and was repeatedly negative for tubercle bacilli. There was a definite clearing of râles on left side with persistence of impaired resonance, altered breath sounds and few medium crackling râles and rhonchi remaining.

*X-ray examination.* This (Fig. 2a) showed mediastinum shifted to the left with whorl-like shadows throughout the whole left lung, similar to those seen in Case 1. Iodized oil was then injected and the X-ray (Fig. 2b) showed very peculiar thin-walled cavities similar to those seen in Case 1 after iodized oil had been injected.

This case appears similar in many respects to the previous one. It is probable that when the patient was two years of age he had massive collapse of the left lung due to central bronchial obstruction, by a foreign body. This resulted in a widespread infection in the bronchi and atelectatic parenchyma. After the central obstruction was removed by the expulsion of the plum stone, the parenchyma failed to become inflated again because of fibrosis or, more likely, on account of terminal bronchial occlusion which will be shown later to be the common cause of continued atelectasis in bronchiectasis. The bronchial walls were weakened by the infectious process and became permanently dilated or bronchiectatic. However, with the relief of the central obstruction and subsequent drainage, the bronchi became clinically non-infected and all cough and sputum disappeared until a fresh infection was added to the dilated bronchi eighteen years later at the time of his influenzal infection. It is possible, of course, that the bronchiectasis was not related to the atelectasis which occurred when the patient was 2 years of age, but that it arose as a result of the influenzal attack when he was 20 years old. Against this hypothesis are the following facts: that the bronchiectasis is on the side where the central obstruction occurred; that the disease is uniform from apex to base with no disease on the other side; and that the mediastinum is shifted. Also, the plain X-ray photographs and those after the injection of iodized oil are similar to those of Case 1, where there is no history suggesting infection as an aetiological factor, and it seems likely that no functioning parenchyma has existed.

Cases 3, 4, and 5 show massive one-sided bronchiectasis in which there is evidence of considerable infection with no history of central obstruction. They are assumed to be cases of acquired bronchiectasis with accompanying massive atelectasis.

*Case 3.* A. G., aged 7, was first observed in 1931 at the Hospital for Sick Children, Toronto, and is included in this report through the courtesy of Dr. Alan Brown. The child was brought to the hospital because he had had a cough with slight purulent sputum, occasionally blood-tinged, and night sweats for two months. There was a previous history of chest trouble for which the child was treated while living in Yugoslavia. The details of this history unfortunately could not be obtained. There was no acute lung disease, such as pneumonia, at the beginning of his illness. He had never had measles or

whooping-cough. The sputum was always small in amount—less than one ounce—and did not have a foetid odour.

*Physical examination.* The child did not appear acutely ill. Chest examination showed diminished movement on the left side with trachea shifted to the left, and left border of the heart in the mid-axillary line; slightly impaired resonance on the whole of the left side with harsh broncho-vesicular breath sounds, bronchophony and many medium crackling râles and rhonchi. The right side appeared normal. The intracutaneous tuberculin test was markedly positive.

The plain X-ray photograph (Fig. 3a) showed the typical whorl-like shadows from apex to base on the left side with mediastinum markedly shifted to that side. There was a small nodule at the left apex apparently representing a primary tuberculous lesion.

Bronchoscopic examination revealed no foreign body or bronchial obstruction. The mucosa of the bronchi on the left side appeared infected. Iodized oil was injected and showed (Fig. 3b) many bronchiectatic cavities from apex to base. Sputum obtained from the bronchiectatic lung at the time of the bronchoscopic examination did not reveal tubercle bacilli by direct smear or guinea-pig inoculation. Culture of the sputum showed haemolytic streptococci and *Staphylococcus aureus*.

The child has been under observation until February 1934, and has shown no essential change in symptoms and physical signs, neither on X-ray nor bronchoscopic examination.

*Case 4.* H. P., aged 14, admitted to the medical wards, Toronto General Hospital, November 5, 1929. His mother stated that he had never been healthy. At 3 years of age he began to cough and had done so ever since. At the age of 4 he had had measles with some chest complication and was ill in bed for two months. He often vomited large quantities of chunky yellow sputum after a coughing spell. He had had only moderately good health and had been troubled with constant cough and sputum, fatigue and shortness of breath on exertion. For these symptoms he was admitted to hospital for investigation and study.

*Physical examination.* He was not acutely ill. The chest showed retraction on left side with diminished movement; diminished resonance throughout; marked shift of trachea to left with left border of heart in left mid axillary line. Bronchial breath sounds were heard over entire left chest with showers of fine and medium crackling râles, increased by cough. The right lung showed nothing abnormal. No clubbing of fingers.

Temperature normal. Sputum persistently negative for tubercle bacilli and not foetid. X-ray examination showed the whorl-like arrangement from apex to base, with very marked shift of the mediastinum to the affected side.

*Case 5.* D. P., aged 36, admitted to hospital as a case of pneumonia, December 15, 1932. The previous day the patient suddenly felt very ill, feverish, and short of breath. His respiratory history went back to 1914, when he was 18 years of age, at which time he began to have repeated 'chest colds' for one and a half years and then some spitting of blood. Since then he has had almost constant cough with yellow chunky sputum, not offensive and never exceeding 4 oz. in twenty-four hours. The sputum had

been examined repeatedly since for tubercle bacilli, with negative results. Since 1914 he had had repeated exacerbations of his pulmonary infection, pneumonia being diagnosed on several occasions.

*Physical examination.* He appeared very ill; temperature  $102^{\circ}$ ; some respiratory distress. Examination of his chest showed marked shift of mediastinum to left, impaired resonance on whole left side, with bronchial breath sounds and bronchophony. Many medium crackling râles were heard from apex to base. The right lung appeared normal.

The temperature became normal in two weeks and the patient felt as well as before the acute exacerbation. Cough and sputum continued. On discharge, physical examination of the chest was the same as on admission except that there was a marked decrease in the number of râles heard. Physical examination for three years before this admission to hospital was identical with that on discharge. X-ray examination on admission and at time of discharge showed marked shift of the mediastinum to the left with the peculiar whorl-like arrangement of shadows from apex to base, with no evidence of disease in the other lung. After the injection of iodized oil, cavities were seen from apex to base similar to those seen in the other cases.

In Cases 3, 4, and 5, it is thought that the initial parenchymal change is atelectatic rather than fibrotic in character. The reasons for this are: that the disease is uniform from apex to base; that there is not the irregular distribution of fibrosis commonly found in basal bronchiectasis with extension; that the other lung is clear: that the mediastinum is shifted to the affected side.

While it is possible in these cases that congenital atelectatic bronchiectasis has been present without symptoms since birth until the dilated bronchi became infected, there is no proof. Acquired bronchiectasis is a more likely diagnosis because it appears to be much more common and to be associated with a history of prolonged infection in the bronchiectatic area, such as was present in these cases. The cause of this atelectasis of an entire lung with bronchiectasis is probably the same as that which produces acquired lobar atelectasis with bronchiectasis. Recent advances in our knowledge of the production of acquired atelectatic bronchiectatic lobes may be applied to the whole lung. A mechanism similar to that described by Warner and Graham (1) as the common cause of lobar atelectasis in bronchiectasis may be responsible also for massive atelectasis. It has been shown in many cases that the cause of the collapsed or shrunken lobe, which is usually triangular in shape, is that the terminal bronchioles become plugged by swelling of the bronchial wall due to inflammatory exudate. This terminal obstruction has been proved to be the cause of the atelectasis in some cases of lobar atelectatic bronchiectasis, and is thought to account for the majority of cases of shrunken lobe producing a triangular roentgenological shadow.

It is likely that massive atelectasis has occurred in Cases 3, 4, and 5 as the result of peripheral bronchial obstruction secondary to infection of the bronchial wall. Fibrosis secondary to infection of the parenchyma has not produced, in the writer's experience, the clinical or X-ray picture of the cases presented here. When fibrosis of the parenchyma has occurred, there

is not the uniformity of disease from apex to base but much more unequal distribution of areas of fibrosis and consolidation.

Whatever the cause of the atelectasis of the parenchyma, the effect on the bronchi is the same. There is a great increase in the negative pressure on the side of the thorax in which the collapse has occurred; and this increase in dilating force, especially if acting on a bronchus whose wall is weakened, will cause permanent dilatation (10).

### *Discussion*

In this series of cases we have endeavoured to show that massive atelectasis of the parenchyma of a lung has probably occurred, and that plain X-ray photographs of the chest show a peculiar whorl-like arrangement of shadows from apex to base, with the mediastinum shifted to the affected side (Fig. 1a).

The parenchymal change occurring in these cases may be fibrotic, secondary to infection in the alveoli. Against this is the fact that in widespread fibrosing infections of the lung with bronchiectasis no such picture is produced. In this type there are marked irregularities in the deposition of the fibrous tissue, and one does not get the uniform picture present in the cases reported here. The plain X-ray photographs of the cases reported here are similar to those found in cases reported by Pinchin and Morlock (11). They believe that their cases represent congenital bronchiectasis with absence of the alveoli. Unfortunately, we have not had the opportunity of examining pathologically lungs from any of these cases, and therefore the proof of atelectasis must be indirect. If we are correct in assuming that the parenchymal change is atelectatic, then an explanation must be made as to how this occurs in acquired bronchiectasis. Some clinicians believe that bronchial dilatation occurs only as the result of the pull of pleural adhesions or of fibrous tissue following inflammatory changes in the parenchyma. The writer's opinion is that neither fibrosis of the parenchyma nor pleural adhesions need be present in these cases, and it must therefore be shown that neither is essential to the production of bronchiectasis.

That bronchiectasis may occur without either fibrosis of the lung or pleural adhesions seems proved by the work of Warner and Graham (1) on lobar atelectasis in bronchiectasis. They agree with Andral (12) and Stokes (13) who first advanced the theory that the bronchus is the structure primarily at fault in bronchiectasis and that the initial change is weakening of the bronchial wall due to infection, with secondary changes in the parenchyma. This is in direct opposition to the theory of Corrigan (14), Hamilton (15) and many followers, that in bronchiectasis the fibrosis of the parenchyma is the primary fault. Warner and Graham have shown by pathological examination of a bronchiectatic lobe removed at operation (lobectomy) that bronchiectasis occurs without any fibrosis of the parenchyma and without any pleural adhesions. Further proof of the occurrence of

bronchiectasis without fibrosis or pleural adhesions was obtained by the same investigators when they observed lobar atelectatic bronchiectasis appear in such a short time that the more chronic process of fibrosis could not account for it. These authors conclude that the primary fault in bronchiectasis is a weakening of the bronchial wall, which can be seen by pathological examination as destruction of the elastic and muscle coats from infection (16).

This study was undertaken in connexion with the investigation of triangular basal shadows on X-ray photographs of the chest in patients suffering from bronchiectasis. It was found that in 6 per cent. of all cases of bronchiectasis triangular-shaped shadows were seen in the cardio-diaphragmatic area (Fig. 4a). Invariably, in our experience, the triangular-shaped shadows have represented a bronchiectatic lobe as proved by the injection of iodized oil into the bronchial tree (Fig. 4b). These triangular basal shadows were first described by Comby (17) as being diagnostic of bronchiectasis, and there has been much discussion as to their aetiology. The triangular shadow represents a shrunken lobe which was thought by Rist, Jacob, and Trocmé (18), Sergent and Bordet (19), Wallgren (20), and others to be due to pleural thickening and inflammatory changes within the lung secondary to primary bronchiectasis. Kerley (21) has recently suggested that these shrunken bronchiectatic lobes are frequently accessory lobes which have become bronchiectatic because of their rudimentary nature. In the cases reported by Warner and Graham bronchoscopic and pathological examinations showed that the atelectatic bronchiectatic lobe is one of the usual lobes of the lung and not an accessory one. Singer and Graham (22) and others believe that the small and triangular-shaped lobe is due to atelectasis, but no adequate explanation for the deflation of the parenchyma was found. There is abundant evidence that the atelectasis of the parenchyma is not usually due to central obstruction, but to obstruction occurring in the terminal bronchioles. This obstruction is caused by the obliteration of the lumen of these bronchioles as the result of swelling of the bronchial wall from inflammatory reaction in it.

It is, therefore, obvious that bronchiectasis can occur without fibrosis or pleural adhesions; also, that the common cause of acquired atelectasis associated with bronchiectasis is a plugging of the terminal bronchioles. So in the cases reported here of probable atelectasis involving an entire lung, the parenchyma was not necessarily fibrosed. Also, there appears to be no reason why that process should not involve a whole lung.

In lobar atelectatic bronchiectasis, central bronchial obstruction is occasionally the cause of both the atelectasis and the bronchiectasis (20). The same may occur in a whole lung, and in Case 2 there is a certain amount of evidence to suggest that obstruction of the main bronchus to the left lung was the original cause of the atelectasis and bronchial dilatation. We believe that central bronchial obstruction plays a minor part, and that by far the commonest cause of massive atelectasis in bronchiectasis is occlusion of the

terminal bronchioles by swelling of the bronchial wall. It is suggested that this is the cause of atelectasis of the parenchyma in Cases 3, 4, and 5.

Atelectasis of the parenchyma is a big factor in the establishment of permanent bronchial dilatation and in the continuance of the bronchiectasis. The deflation of the parenchyma causes a markedly increased negative pressure in that side of the thorax, which increases the dilating force on the bronchial wall (10). Also, when atelectasis of the parenchyma is present, the movements of the bronchi, which are so essential to proper drainage of secretion, are interfered with and, consequently, stagnation of secretion in the lumen of the bronchi occurs, which tends to aggravate and continue the bronchiectasis.

Atelectasis of the parenchyma in bronchiectasis is of importance because it produces changes on physical and X-ray examination which aid in the diagnosis of bronchiectasis. This is true of lobar atelectasis where the triangular basal shadow in the radiograph is practically diagnostic of an atelectatic bronchiectatic lobe. It is also equally true of the cases of massive atelectasis of the parenchyma of one lung in the cases described above. In massive atelectatic bronchiectasis, the plain X-ray photograph is distinctive in showing thin whorl-like shadows from apex to base with mediastinum shifted to the affected side.

Another point which we believe the discussion of these cases of so-called massive atelectatic bronchiectasis brings out is that congenital bronchiectasis is a pathological curiosity. A review of the pathology of congenital bronchiectasis leads to the conclusion that it can be diagnosed positively only if found in a foetus or new-born babe. Case 1 is presented as a case of congenital massive atelectatic bronchiectasis because of an exceptional history and very little evidence of inflammatory reaction in the lung. It seems almost impossible to diagnose congenital bronchiectasis clinically with any degree of certainty in a person more than two or three weeks of age.

### *Conclusions*

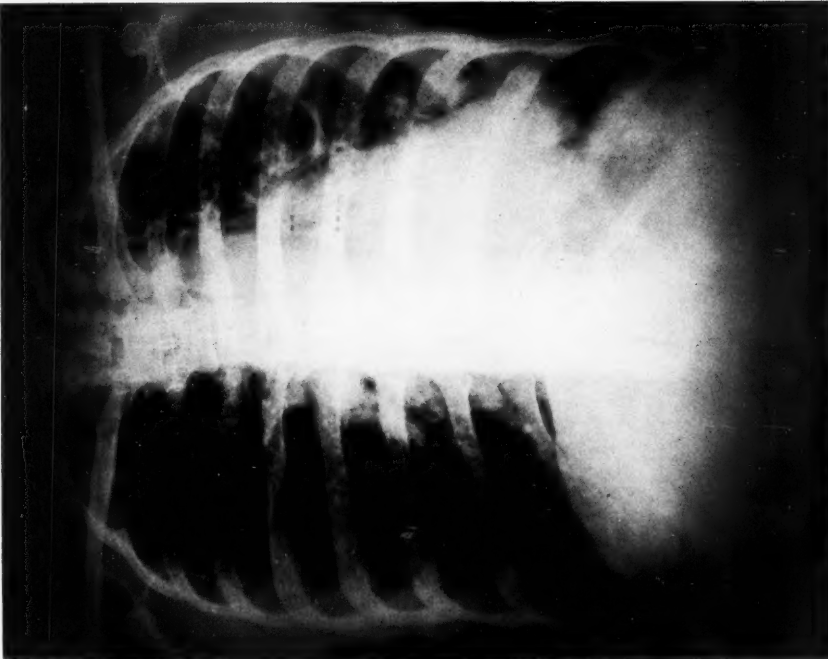
1. Five cases of bronchiectasis involving a whole lung are reported in which it is assumed there has been massive atelectasis.
2. One case is considered congenital in origin.
3. Another case is possibly due primarily to central bronchial obstruction.
4. The atelectasis in the remaining cases of acquired massive atelectatic bronchiectasis is probably due to obstruction of the terminal bronchioles.
5. Fibrosis of the parenchyma and pleural adhesions are not necessary for the production of bronchiectasis.
6. Atelectasis is a factor in the production and continuance of bronchiectasis.
7. A provisional diagnosis of massive atelectatic bronchiectasis may be made from plain X-ray photographs because of the uniform changes from apex to base and the thin-walled whorl-like shadows.

8. Congenital bronchiectasis is a pathological curiosity. It should be diagnosed with a great deal of hesitation in a patient over a few weeks of age.

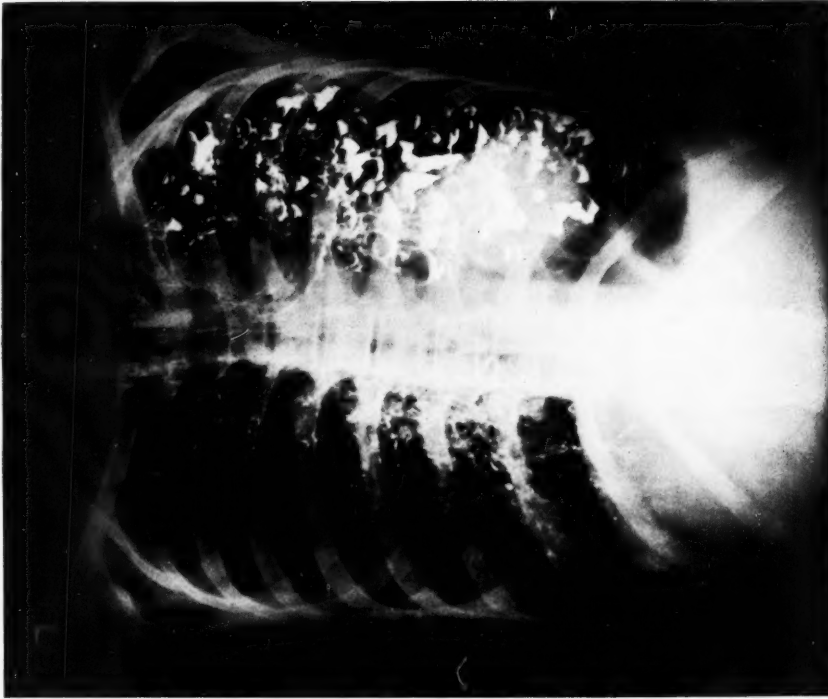
The author gratefully acknowledges the assistance and advice of Professor Duncan Graham in this work.

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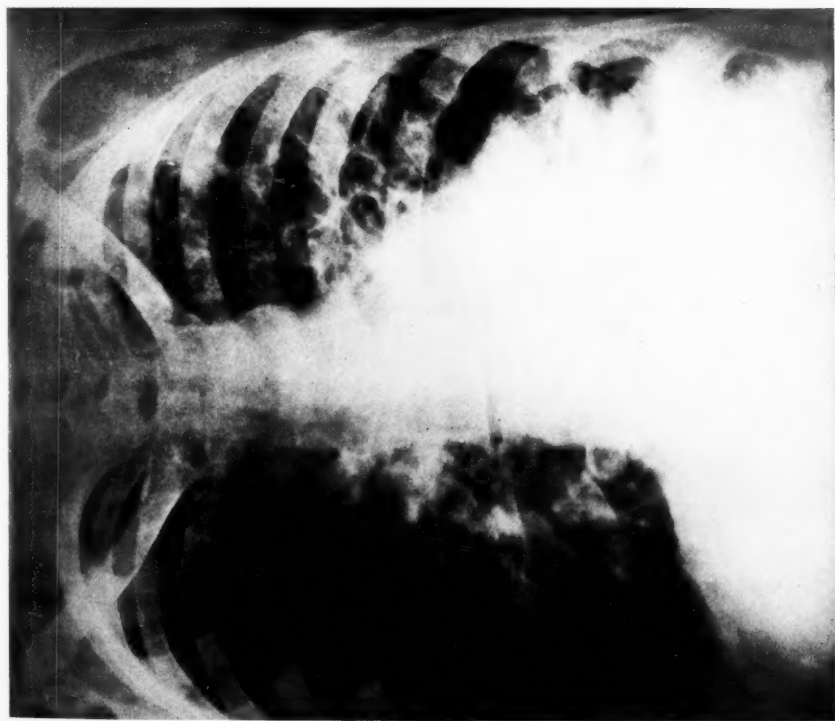
*a.* Plain radiograph, showing evenly distributed thin whorl-like shadows from apex to base with mediastinum shifted to the affected side



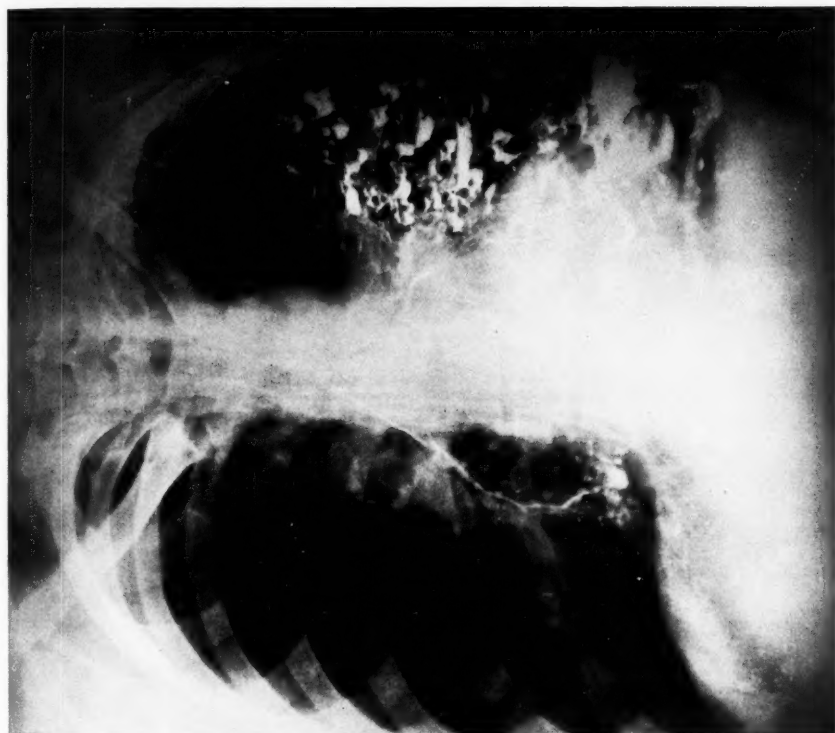
*b.* After the injection of iodized oil, showing peculiarly shaped cavities from apex to base

FIG. 1. Massive atelectatic bronchiectasis, possibly congenital





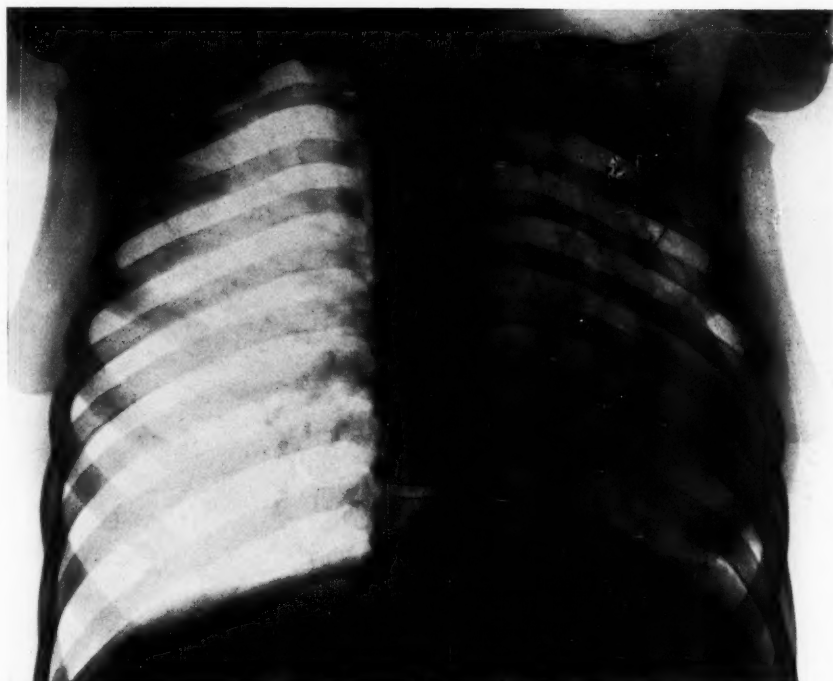
*a.* Plain radiograph, showing whorl-like shadows evenly distributed which are characteristic of this type of bronchiectasis



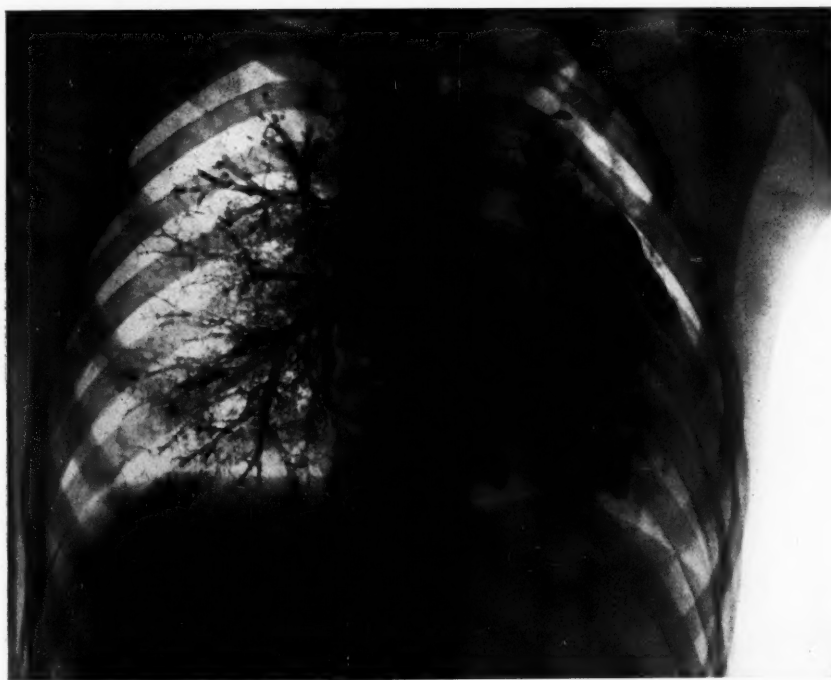
*b.* Saccular dilatations visualized after the injection of iodized oil possibly resulting from central bronchial obstruction

FIG. 2. Massive atelectatic bronchiectasis, possibly resulting from central bronchial obstruction





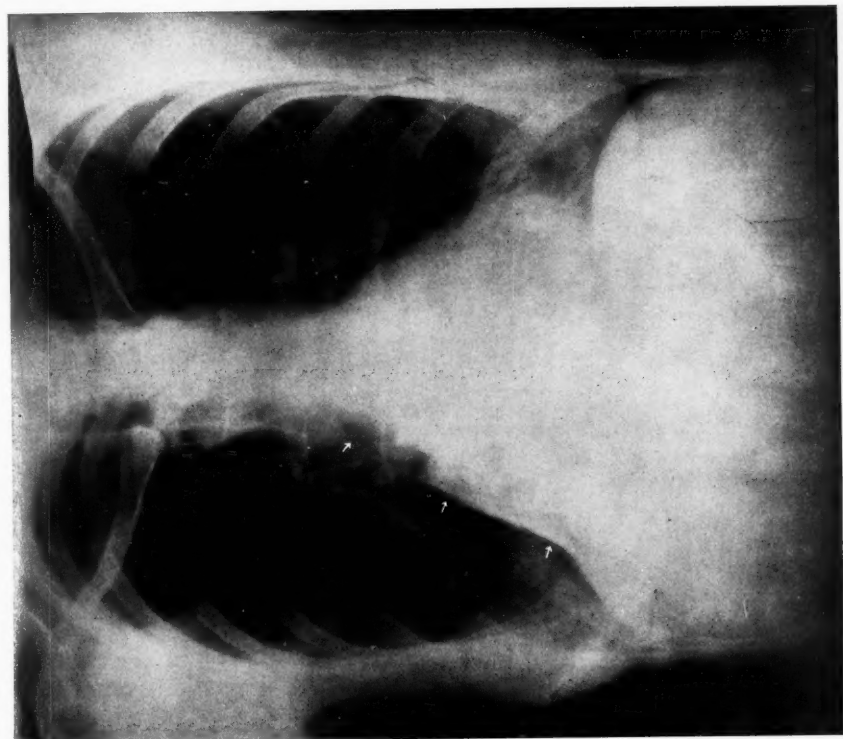
*a.* Plain X-ray photograph, showing whorl-like shadows from apex to base, diagnostic of bronchiectasis



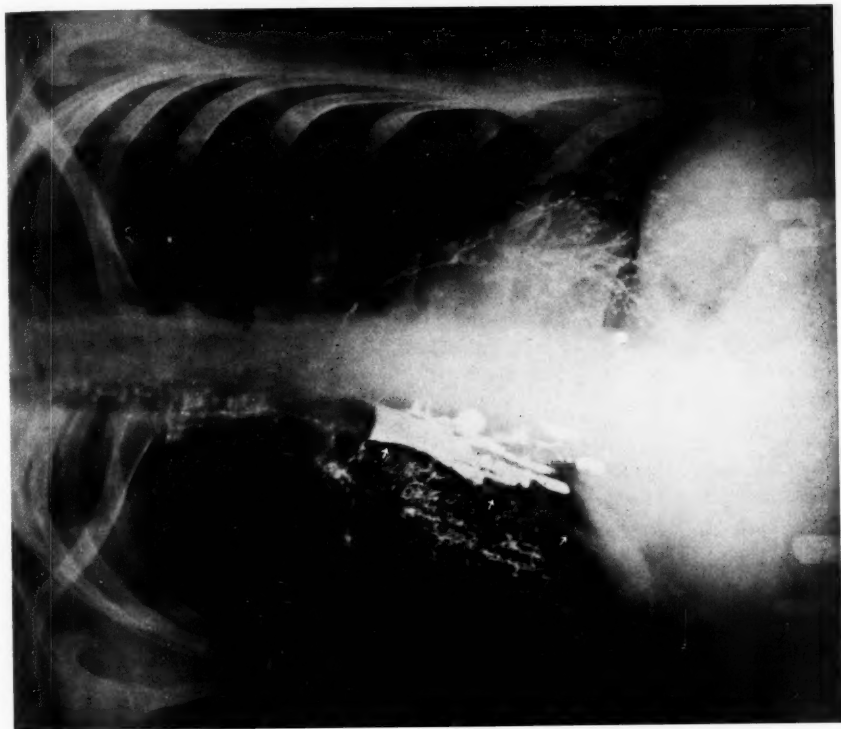
*b.* Same case with iodized oil injected through the bronchoscope

**FIG. 3.** Acquired massive atelectatic bronchiectasis



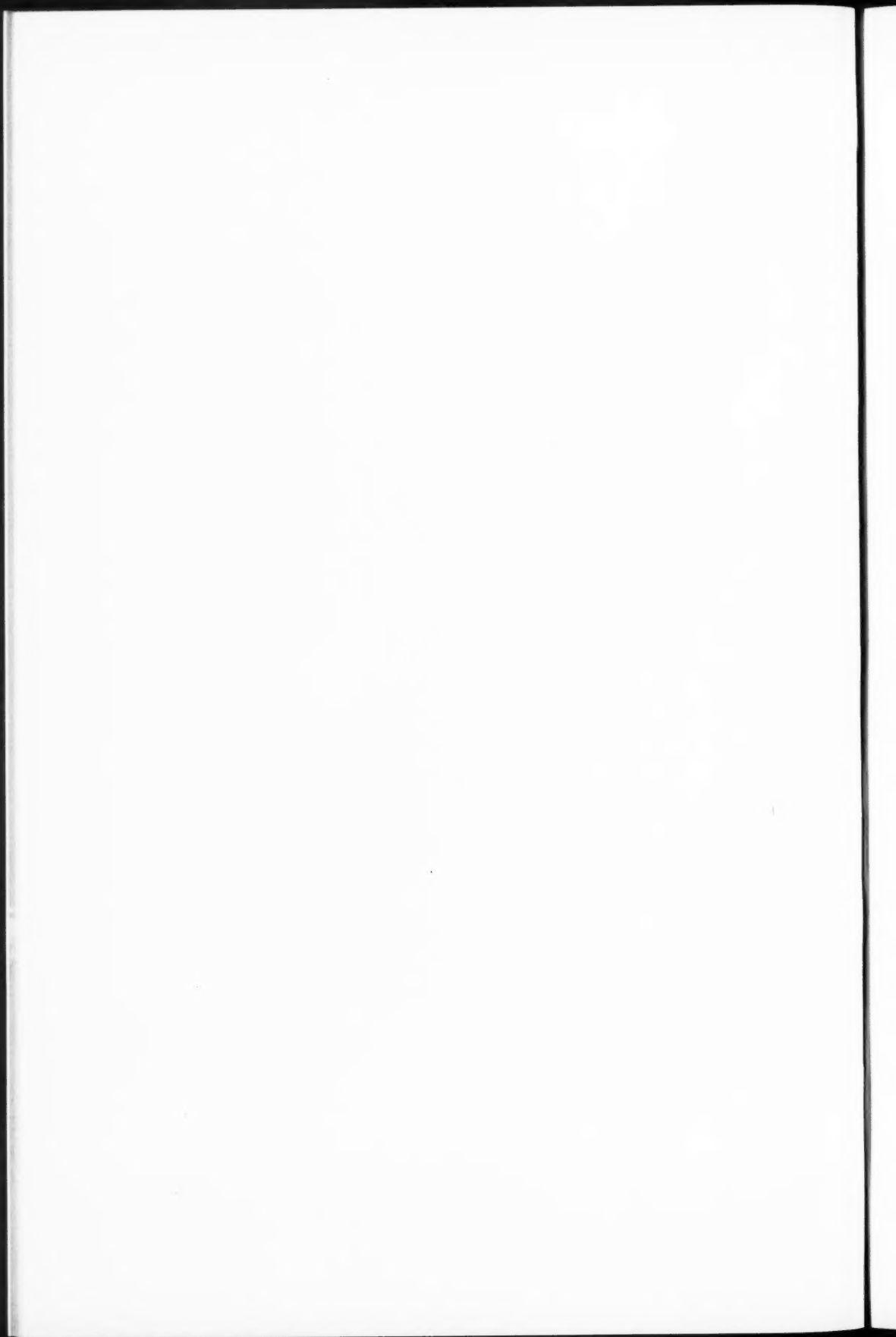


*a.* Plain radiograph, showing triangular basal shadow in costodiaphragmatic area, which is diagnostic of bronchiectasis



*b.* After the injection of iodized oil into the bronchial tree, showing the main bronchus to the right lower lobe communicating with dilated bronchi which are only seen in the area of the shadows

FIG. 4. Lobar atelectatic bronchiectasis



## THE TREATMENT OF MUSCULAR DYSTROPHY WITH GLYCINE<sup>1</sup>

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In 1931 one of us (D. P. C.) had the privilege of working in Prof. Karl Thomas' laboratory in Leipzig, and there came in contact with the researches of Thomas and his co-workers Milhorat and Techner on the beneficial effect of glycine on the course of progressive muscular dystrophies. On the publication of their first paper in 1932, experiments on similar lines were commenced in the department at Glasgow.

As early as 1907 Spriggs had observed that 'creatinine is excreted in smaller quantity than normal when the bulk of the muscular tissue is diminished, as in the primary myopathies; also when muscular activity and muscular tone are depressed by a pathological condition of the muscle or motor apparatus, as in myasthenia gravis and amyotonia congenita'. The majority of workers (Rosenthal (32); Levene and Kristeller (23); Janney, Goodhart, and Isaacson (19); Bürger (11); Meyer (24); and Gibson, Martin, and Buell (16)), have found such low values in muscular dystrophy.

A creatinuria has been noted in many diseases which primarily or secondarily attack the muscular system, and the foregoing workers have found this to occur in muscular dystrophy.

When creatine is given to normal adult persons in amounts not exceeding 1 gm. per day it is practically wholly retained within the organism (Klercker (20); and Folin (14)). Levene and Kristeller (23), Gibson and Martin (15), and Williams and Dyke (38), have found that in subjects of certain muscular diseases much less creatine is retained. Gibson and Martin obtained complete recovery in the urine in a case of progressive muscular dystrophy, and Milhorat, Techner, and Thomas (26) found in their cases of progressive muscular dystrophy almost quantitative excretion of ingested creatine (65-100 per cent. of 2.64 gm. anhydrous substance).

In addition to creatine Gibson and Martin found that gelatine and glycocyamine increased the creatinuria in these cases. Brand, Harris, Sandberg, and Ringer (8), and Lasker (9), found that the ingestion of glycine as well as glycocyamine resulted in an increased excretion of creatine—4-8 per cent. going over to creatine. This relationship led Thomas and his co-workers to investigate the effect of prolonged administration of glycine on the clinical course of progressive muscle dystrophies.

In their preliminary reports it was stated that the ingestion of 15-20 gm. glycine daily raised the creatinuria of the different cases by different degrees

<sup>1</sup> Received January 2, 1934.

depending on the extent of the original creatinuria. After a period of some weeks (depending on how advanced the case was) the creatinurias were found to decrease despite the continuance of glycine, until the former control level was reached. In one advanced case even after eight weeks the previous level had not been reached. The creatinuria in one patient fell to a level lower than the original. Coincident with the decrease in the creatinuria there was a rise in the creatinine output and an improvement in the patient's ability to hold ingested creatine. These changes relapsed on the cessation of therapy. It was also reported that the patients improved in a remarkable manner coincident with these chemical changes. On ceasing to give glycine they relapsed.

While control studies on cases showing extensive muscular atrophy from other causes showed a creatinuria on a creatine free-diet and a failure to retain ingested creatine (50 per cent.), there was no increase in the creatinuria following glycine and no clinical improvement. Thomas and his colleagues concluded from their preliminary studies that the improvement obtained in their cases of progressive muscular dystrophy and pseudohypertrophic muscular dystrophy was not due to any temporary irritative action of this amino acid, but that glycine played a significant role in the pathogenesis and treatment of the disease.

Since the publication of these preliminary papers Remen (29) and Boothby (4, 5, 6, 7) have extended the use of glycine with definite benefit to the treatment of myasthenia gravis. Of his cases of muscular dystrophy Boothby (4, 5) reported as yet only a little progress in two of the four cases studied: 'even in these two the improvement was not enough to be beyond question'.

More recently Milhorat has published (27) fuller details of the original cases and data of new cases—in all fourteen cases of progressive muscular dystrophy. He noted that a case of amyotonia congenita and another case of a similar nature were benefited by glycine. Histological examination of portions of muscle obtained by biopsy indicated that whereas prior to glycine therapy there were atrophied, partially atrophied, and normal fibres present, after glycine there were no partially atrophied fibres, the presumption being that those incompletely atrophied had recovered.

An analysis of Milhorat's clinical records indicates that there was very marked improvement in only two cases (1 and 3) and slight improvement in one other. The remaining nine cases appeared to have remained stationary or regressed. In a personal communication Thomas states that in his view improvement is only possible in the partially atrophied fibres, and that in those quiescent cases where only atrophied and normal fibres might be found, no improvement could result from glycine therapy.

Brand and Harris (10) have pointed out that the Cases 1 and 3 described by Milhorat as having improved so well had creatinurias (here expressed as creatinine *N*) amounting to only 0.011 and 0.0074 grm. daily (respectively a third and a fourth of the value of our lowest recorded creatinuria). They suspect that Milhorat's cases may belong to a special clinical group which respond to glycine therapy, for in nine cases of muscular dystrophy treated with glycine (7.5–25 grm. daily) for a prolonged period (2–9 months) in patients ranging from 8–24 years of age and presenting various grades of severity, no favourable effect such as had been described by the German workers was noted. Boothby considers that Milhorat's Cases 1 and 3 may have been examples of myasthenia gravis.<sup>2</sup> Brand and Harris found no

<sup>2</sup> In a personal communication (18.6.34) Prof. Thomas states that he is convinced of the accuracy of their original diagnosis of these cases. Case I has been observed by many clinicians over a period of years without question being raised as to the diagnosis.

improvement in one case of myasthenia gravis. In a subsequent report on these cases Harris and Brand (17) point out how difficult it was to ascertain whether any slight improvement had occurred owing to the lack of satisfactory methods for measuring such improvements. 'A number of cases improved markedly in their nutritional states during the period of treatment with glycine. Their disabilities, however, appear to have remained practically unchanged. Only one fairly advanced case became worse.'

Adams (1) fed glycine and glycine with ephedrine to healthy persons, to patients with myasthenia gravis, and to patients with muscular dystrophies. The increase in excreted creatine appeared to be influenced by the degree of creatinuria before glycine therapy. The results of a balanced experiment on a patient with myasthenia gravis showed no decided change in the N, P, or S, balance on feeding glycine.

Beard and Tripoli (2) report the treatment of a case of 'neuromuscular dystrophy', a case of progressive muscular dystrophy and a case of 'psychopathic inferiority complex'. At the time of their publication all the patients were slowly recovering their strength and were gaining in body weight. These findings were stated to be in agreement with about twenty similar cases being treated at the same time. A marked initial creatinuria, disappearing in a few days, was noted.

The reaction to glycine of five cases of progressive muscular dystrophy, in one family, was reported as favourable by Chanutin, Butt, and Royster (12), Voshell (37) on the other hand was unable to arrive at any definite opinion as to the therapeutic merits of pilocarpine and epinephrine and glycine.

Kostakow and Slauck (21, 22) confirm, in their series of nine cases of progressive muscular dystrophy, the general clinical and chemical changes noted by Thomas and his co-workers. They noted, as did Brand *et al.* and Thomas *et al.* that the ingested glycine appeared to be only in part converted into extra creatine.

Reinhold, Clark, Kingsley, Custer, and McConnell (28) studied nine cases of progressive muscular atrophy for periods up to fourteen months. 'Little tangible evidence of improvement in muscular function has been obtained. Muscle specimens removed at biopsy after treatment with glycine were distinctly better in quality, chemically and histologically, than similar specimens taken before treatment. Restoration of various characteristic muscle components accompanied regeneration of the muscle fibres.' 'Despite this improvement in structure and composition . . . a great disparity with the normal remained, probably sufficient in many cases to account for the failure of muscular function to be restored to a greater extent.' On examining the protocols it may be noted that in two out of the six cases in whom biopsies had been performed before and after treatment with glycine, the chemical and microscopical findings were at variance.

We have not had the opportunity of studying the effect of glycine on myasthenia gravis. We have, however, made observations on a few normal persons and on nine cases of progressive muscular dystrophy and two other cases exhibiting marked selective muscular atrophy.

#### *General Plan of Experiments*

A series of nine cases of muscular dystrophy of different types and two other cases exhibiting selective muscular atrophy were subjected to prolonged periods of glycine therapy.

TABLE I

Source.	Condition (No. of cases).	Age Yrs.	* Preformed creatinine N. mg.	Creatine N. mg. (as creatinine).	Creatinine coefficient.	Creatine fed gm. $\times$ days fed.	% Creatine retained.	Glycine fed daily.	Rise in creatinine N. mg.
Harris and Brand (1933)	Normal children (4)	9-10	164-192	30-70	5.2-6.8	$0.3 \times 1$	60	—	—
	Normal males (36)	20-40	410-733	0-74	6.2-18.2	$0.5 \times 2$ (5 cases)	100	7.5 (3 cases)	0
	Normal females, average (66)	20-40	196-644	0-37	3.5-9.6	$0.5 \times 2$ (3 cases)	100	7.5 (1 case)	0
	Muscular (16)	—	440-633	0-74	7.6-10.2	—	—	—	—
Folin (1906)	Normal males (2)	—	566-677	—	—	$4.4 \times 1$	47-81	—	—
Meyers and Fine (1915)	Normal (1)	—	492	—	—	$0.97 \times 1$	100	—	—
	Normal male (1)	—	499	—	—	$1 \times 1$	100	—	—
	Normal male (1)	—	478	—	—	$2 \times 1$	84	—	—
						$3 \times 1$	76	—	—
						$4 \times 1$	73	—	—
Rose and Dimmitt (1916)	Normal	—	499	—	—	$5 \times 1$	78	—	—
						$1 \times 1$	80	—	—
						$2 \times 1$	71	—	—
						$3 \times 1$	69	—	—
						$4 \times 1$	63	—	—
						$5 \times 1$	61	—	—
						$1 \times 1$	79	—	—
						$2 \times 1$	84	—	—
						$5 \times 1$	58	—	—
						—	69 (1 case)	—	—
Present authors	Normal children (2)	12-14	74-79	63-165	1.8-3.0	$2.64 \times 1$	37	12	0
	Adolescent female (1)	16	252	21	5.2	$2.64 \times 1$	37	12	38
	Normal male (1)	23	213	159*	3.0	$4.4 \times 1$	84	15	0
	Early disseminated sclerosis (1)	35	306	123	4.5	$4.4 \times 1$	80.5	15	0

Harris and Brand (1933)	25	407	74	6.7	0.25	60	15	74
Periodic familial paralysis (1)	9-28	111-370	37-149	4.2-6.6	(0.2-0.5) × (6-9)	45-60	7.5-10	0-48
Charcot Marie Tooth (3)	18-41	260-330	55-74	6.2-6.4	1 × 5 (1 case)	63 (1 case)	15-22	0-37
Myasthenia gravis (2)	19	555	96	10.0	0.4 × 7	100	15	0
Hemiatrophy (1)	7	166	18	6.5	0.5 × 4	70	7.5-15	34
Post encephalitis (1)	39	407	185	6.1	—	—	15	0
Amyotrophic lateral sclerosis (1)	35	462	18	7.5	2.0 × 6	100	—	—
Multiple sclerosis (1)	25	407	74	8.2	2.0 × 2	100	15	0
Muscular atrophy (1)	68	130	26	3.0	2.62 × 1	76	15	4
Arthritis deformans with advancing muscular atrophy (1)	52	240	11	3.4	2.62 × 1 2.62 × 1 (after gly- cine)	42.5 48.5	— 15	— 26
Spastic spinal para- lysis muscular atrophy (1)	25	196	11	4.2	2.62	51	15	0
Little's disease ad- vancing muscular atrophy (1)	28	407	44	7.0	—	—	15	0
Progressive spinal atrophy (1)								

\* No clinical reason could be advanced for this high creatinuria.

The Wassermann reaction was negative in the blood of all these patients, and the spinal fluid in each case proved normal when examined in respect of protein content, cell count and the Wassermann and colloidal gold tests. No patient was suffering from any associated disease which might have been considered to minimize the effect of treatment, except Case 8, a boy, who had an otorrhoea which required radical treatment. This patient, however, showed greater general improvement than the others.

During the course of glycine treatment, there was no massage, electrical, or tonic treatment given, the patients being allowed up and encouraged to exercise themselves in the wards and out of doors according to their powers. They were asked to observe their condition and to describe any sensation or improvement. On admission to the wards of the Biochemical Department, the patients were put on a basal diet free from meat, meat extract, and fish.

These diets consisted of 110-190 gm. white bread; 45-92 gm. butter; 100-150 gm. egg; 660-1040 c.c. milk; 200 c.c. meat extract free soup; 50-100 gm. potato; 30-50 gm. peas; 30-70 gm. carrot; 50-100 gm. cabbage; 1 orange; 0-40 gm. cheese; 30-60 gm. pear; 40-60 gm. wheaten biscuit and 0-100 gm. prunes. The protein content of the diets varied in the adults from 56 to 80 gm. per day; in the case of the children from 53-72 gm. per day.

The total creatinine and preformed creatinine outputs were estimated in the twenty-four hourly specimens of urine which were preserved with thymol in chloroform. Total creatinine was determined by the method of Benedict (3); preformed creatinine by Folin's method (14). The difference between these two estimations represents the quantity of creatine excreted. At various intervals the patient's reaction to ingested creatine was determined. During these periods no glycine was taken. The amounts excreted are expressed as mg. N. per day. Unless where specially noted the glycine was supplied by British Drug Houses Ltd. Certain of the cases received in addition glycine supplied by Baeyer-Meister, Lucius and Brüning; these cases are marked by asterisks.

Generally three to four days after the first dose of creatine, glycine therapy was commenced. The adults received 15 gm. daily, the children 10 gm. daily, dissolved in milk. This was given as one dose.

When urine was not being collected the patients were put on ordinary diet. The patients' weights were recorded weekly, as also their performance in time and generally on stairs or other exercises involving use of the affected muscles. Wherever possible the power of the affected muscles was gauged by movement of each joint against gravity or against the observer's finger. Rising from recumbency, from touching the toes, and from a chair were employed to gauge progress; so too was the power to lift weights. As it would be impossible to present in detail all our clinical observations, we are forced to give our personal summary of changes in the state of these cases and only occasionally to amplify these statements by description of the condition of the individual muscles.

*Experimental Data*

In Table I are contained in summarized form data relative to the effect of ingested creatine and glycine on the urinary excretion of creatine and creatinine in both normal and diseased subjects. No case of progressive muscular atrophy is included in this selection abstracted from the records of Harris and Brand (17), Folin (14), Meyers and Fine (25), Rose and Dimmitt (31), Milhorat (26), and ourselves.

Of the nine cases of muscular dystrophy to be described, Nos. 4 to 8 inclusive were of the pseudo-hypertrophic type. No urinary studies were made on the ninth case, and therefore it does not appear in Table II.

*Case 1. Muscular dystrophy.*

W. S., Female, aged 24, was admitted in March 1933. She complained of inability to raise her arms above her head, of difficulty in ascending stairs, and of breathlessness on exertion.

The weakness of the legs manifested itself in climbing stairs at the age of thirteen, and two years later she had difficulty in holding up her arms. Since then there had been remissions and exacerbations in her condition, but in the last year both arms and legs had become steadily weaker and she had been aware for two years that she became breathless on slight exertion. She had been working, however, till her admission. There was no familial history of dystrophy and there was no pseudo-hypertrophy. She could not raise her arms to the level of her shoulder, and could only climb stairs very slowly with the aid of the rail and with the right foot leading. Even in bed, examination of her muscular system made her breathless. She needed the assistance of her hands placed above her knees in order to rise from the recumbent position. After ten days' rest in bed, on general tonic treatment only, she had regained considerable power, and could climb stairs without the aid of the rail and with the feet leading alternately. She could raise her arms above her head, but could not make the hands touch. She continued to make slight improvement. The patient was given glycine from 27th May to 14th June. During this period she made only slight further improvement in the specific muscles affected, but as she was afraid of losing her post she asked to be discharged. After a short holiday she resumed work on 23rd June and stated she felt quite fit for a week. She then became breathless, even on the level, and required the aid of her arms on stairs. Her arms became weaker in raising them to or above her shoulders. She reported and was readmitted on 21st July, and was found then to be almost as weak as on her original admission; but again improved from rest in bed only. She had glycine from 8.8.33 to 19.9.33 and made considerable general improvement, gaining 2.7 kg. in weight. She could climb stairs much more quickly and movement at the hips was stronger. Abduction at the shoulder was stronger. Dyspnoea was noted, even on slight exertion, and she tired easily. Three electrocardiographic tracings taken during the period of six months showed nothing notably abnormal. She had no pulmonary disease.

She was discharged on 16.11.33, fifty-eight days after glycine treatment was discontinued. Her general improvement and feeling of well-being was maintained, and movement at the hips was still stronger as also flexion at the left elbow. She was still breathless on slight exertion and her cardiac efficiency was poor as judged by her response to exercise.

*Case 1. 41.3 kg.*

	No. of days.	Average daily excretion.		Remarks.
		Creatin- ine N. mg.	Creatine N. mg.	
Basal diet	3	211	58	
Basal diet + 4.4 gm. anhydrous creatine	1	223	741	45 % creatine retained (first 3 days)
Basal diet	1	220	133	
" "	1	208	83	
" "	16	192	66	
Basal diet + 15 gm. glycine	4	195	94	Maximum creatinuria
" "	4	229	103	(N.) 142 mg. observed
" "	4	233	89	on 5th day following
" "	4	235	51	glycine
Ordinary diet + 15 gm. glycine	4	—	—	
Ordinary diet	35	—	—	At home.
Basal diet + 15 gm. glycine	3*	315	212	Maximum creatinuria
" "	5*	276	73	(N.) 308 mg. noted
" "	5*	256	97	on 2nd day following
" "	5*	257	61	glycine
" "	15	238	69	
" "	3	238	23	
Basal diet + 4.4 gm. creatine	1	244	664	41 % creatine retained
Basal diet	1	224	156	(first 3 days)
" "	1	216	93	
" "	4	209	57	

*Case 2. Muscular dystrophy.*

Mrs. P., aged 38, complained of inability to stoop without collapsing, and weakness in the arms and legs.

She had walked with an erect and stiff gait since 1922, but had only become aware in 1926 of difficulty in picking things off the floor. Since 1928 she had difficulty in climbing stairs and in rising from a chair. She was aware of weakness in raising the arms. In three generations the only history of dystrophy is the affection of a sister.

She had a marked lordosis and lumbar scoliosis. The right foot was slightly abducted, and when she hurried she dragged that foot. She could not rise from a chair without the aid of her arms. The grasp, flexion, and extension at elbow and abduction of the arm were weak on the right side. Power of the right serratus was impaired and the right latissimus dorsi was also weak.

This patient could not sit up in bed without assistance, and from the recumbent position rose in the manner characteristic of her affection. Flexion and extension of the right knee were weak and flexion of the left knee was impaired. She could not raise either leg off the bed when recumbent and could not dig the heels of the extended legs into the bed. Abduction of the legs was impossible, and only the left could be abducted slightly. The reflexes of the right arm and the right knee were absent.

After glycine she became generally much stronger and gained 6.3 kg. in six months. She experienced a sensation of well-being, and measurements showed increased circumference of all limbs. Movements of the trunk were stronger when in bed, but showed no improvement in inhibiting collapse when bending forward from the perpendicular or rising from the recumbent to the erect position. She could walk more quickly over a test distance, and her time for climbing stairs improved, though she could only ascend

with the left foot leading unless supported on the rail. She could raise the left leg 60° from the bed and the right about 3 inches. Flexion of the knees was stronger. Abduction of the arms at the shoulder was definitely stronger, and extension of the right elbow was more powerful.

The patient reported three months later and stated that she had deteriorated since going home, and that she felt worse about a week after leaving hospital (i.e. after glycine was discontinued). She could not get up so easily from a chair, which had previously presented little difficulty. As measured by her general capacity to do certain tasks the patient considered that she has regressed since going home.

She could now only raise the left leg from the bed two inches and the right not at all. She rose from a chair with increased difficulty. Her time on a test distance and on stairs was worse. The improvement in the right arm had been maintained.

*Case 2. 47.4 kg.*

	No. of days.	Average daily excretion.		Remarks.
		Creatinine N. mg.	Creatine N. mg.	
Basal diet	5	110	108	
Basal diet + 4.4 gm. anhydrous creatine	1	120	512	60% creatine retained (first 2 days)
Basal diet	1	126	261	
" "	3	136	82	
Basal diet + 15 gm. glycine	4	137	108	Maximum creatinuria (N.) 320 mg. observed
" "	4	127	125	on 1st day, then level
" "	3	94	147	fell and gradually
" "	10	—	—	rose to 190 mg. on
" "	5	142	79	9th day following
" "	16	—	—	glycine
" "	12	115	138	Creatine excretion
Basal diet	3	118	140	gradually rose to 240
Ordinary diet	31	—	—	mg. (N.)
Basal diet	2	112	72	
Basal diet + 4.4 gm. creatine	1	146	759	49% creatine retained
Basal diet	1	143	173	(first 2 days)
" "	1	135	112	
" "	6	122	66	
Basal diet + 15 gm. glycine	4	87	137	
" "	5	—	—	
" "	13	—	—	
Basal diet	5	137	112	
Basal diet + 15 gm. glycine	19	141	100	Maximum creatinuria (N.) 168 mg. noted on 3rd day following glycine

*Case 3. Muscular dystrophy of Landouzy-Dejerine type.*

M. G., Female, aged 38, complained of weakness of the arms, unsteadiness, and stiffness of the legs, difficulty in climbing stairs, and thickness of speech, following an attack of influenza which kept her off work for three months in 1929. She stated, however, that she had been unable to wrinkle her brows for as long as she could remember.

On admission in April 1932 she could not move her frontales muscles or whistle. There was a left-sided ptosis, probably in part due to a large

tarsal cyst, and a slight paresis of the left facial muscles. There was slight slurring of the speech. The legs had only become affected in August 1931, but the weakness had increased so that she had to give up work in February 1932. She latterly fell two or three times a day. Dorsiflexion at the ankle was weakly performed. She could not raise either foot from the ground in walking, and felt that the left foot would give way under her. The hand-grasp, movements at the wrist, and pronation and supination were weak. With her arms lying extended by her side in bed she could not raise either forearm off the bed, but extension at the elbow appeared normal. The serrati, external rotators of the shoulder, and the rhomboids acted weakly.

*Case 3. 37.5 kg.*

	No. of days.	Average daily excretion.		Remarks.
		Creatin- ine N. mg.	Creatine N. mg.	
Basal diet	4	111	53	
Basal diet + 4.4 grm. anhydrous creatine	1	100	270	75 % creatine retained (first 3 days)
Basal diet	1	107	110	
" "	1	123	124	
" "	3	113	41	
Basal diet + 15 grm. glycine	3	121	79	Maximum creatinuria (N.) 107 mg. observed on 3rd day following glycine
" "	3	118	81	
Ordinary diet + 15 grm. glycine	43	—	—	
Basal diet	6	—	—	
" "	1	107	45	
Basal diet + 4.4 grm. creatine	1	124	276	80 % creatine retained (first 3 days)
Basal diet	1	97	89	
" "	1	107	55	
Basal diet + 15 grm. glycine	10	100	58	Maximum creatinuria (N.) 88 mg. observed on 8th day following glycine
" "	5	—	—	
Basal diet	8	—	—	
Ordinary diet + 15 grm. glycine	28	—	—	
Basal diet + 15 grm. glycine	4	105	80	
Basal diet	4	—	—	
" "	1	137	63	
Basal diet + 4.4 grm. creatine	1	170	495	62 % creatine retained (first 3 days)
Basal diet	1	154	116	
" "	1	165	105	
Basal diet + 15 grm. glycine	8	148	88	
" "	9	—	—	Maximum creatinuria (N.) 106 mg. observed on 4th day following glycine

She gained some power as regards locomotion after three weeks' rest in bed, and eighteen days after commencing glycine treatment she was able to raise the left forearm about 80° off the bed and slightly wrinkle the lower part of the frontales muscles, while dorsiflexion at the wrists was more strongly performed. Two days later she could whistle, her speech was clearer, and she could touch her shoulder with the fingers of the left hand when in bed. A month later similar improvement was noted in the right arm. External rotation at the shoulders was more powerful, also movement at the wrists. Dorsiflexion of the feet did not show a corresponding gain in power. During her six months' residence in hospital no further specific improvement was noted, but she was generally stronger, more active on her feet and less easily fatigued. She gained 4.8 kg. in weight.

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After glycine therapy was discontinued she regressed very rapidly, although possibly a psychic effect contributed to this in her case. The legs especially were weaker, and she was less secure on her feet. Movements below the elbows were weaker, and she could not raise the right forearm off the bed.

## Case 4. Pseudo-hypertrophic muscular dystrophy.

D. M., Male., aged 35, complained of inability to walk unless he wore a corset, difficulty in extending his head and in raising his arms above the shoulder. The first symptoms were noted at the age of 16. There was no history of familial dystrophy. In addition to the posture and gait typical of this form of dystrophy, he showed weakness of the facial muscles.

When lying in bed the patient was unable to raise his head from the pillow or sit up without the assistance of his hands, which he used as levers under the lumbar spine. He could not rise from a chair without the aid of his arms, and rising from the floor was accomplished in the manner characteristic of this dystrophy. Extension at the hips was weak. He could not raise his arms more than 50° from his side when standing, and the serrati were inactive. The pectoral muscles, the extensors of the elbow, and the right latissimus dorsi were weak.

During his residence of over four months this subject made some general improvement and gained 2.0 kg. in weight. He was able to climb stairs more rapidly and move more easily on the level, but in the muscles specifically affected by the disease no improvement was noted. He did not experience any general feeling of well-being as did the other patients in our series. He was mentally depressed and indicated that he might commit suicide if no benefit resulted from glycine.

## Case 4. 69.4 kg.

	No. of days.	Average daily excretion.		Remarks.
		Creatinine N. mg.	Creatine N. mg.	
Basal diet	5	307	90	
Basal diet + 4.4 grm. anhydrous creatine	1	281	679	41 % creatine retained (first 4 days)
Basal diet	1	276	186	
" "	1	280	172	
" "	1	286	156	
Basal diet + 15 grm. glycine	4	237	133	Creatinuria had not reached basal value before glycine commenced. Maximum creatinuria (N.) 362 mg. noted on 10th day following glycine
" "	4	210	59	
" "	4	184	219	
" "	4	111	222	
" "	5	141	212	
Ordinary diet + 15 grm. glycine	30	—	—	
Basal diet + 15 grm. glycine	12	176	31	
Basal diet	11	210	34	
Basal diet + 4.4 grm. creatine	1	265	355	71 % retained (first 3 days)
Basal diet	1	243	84	
" "	1	232	67	
" "	1	231	23	
" "	1	249	28	
" "	16	—	—	
" "	5	209	38	
Basal diet + 15 grm. glycine	8	204	72	Maximum creatinuria (N.) 218 mg. noted on 5th day following glycine

*Case 5. Pseudo-hypertrophic muscular dystrophy.*

P. McG., Male, aged 26, was admitted in May 1932. The onset was apparently at the age of 15. The extensors of the trunk were first affected. The condition progressed, but he managed to continue his work as an iron-dresser until he was 21. The knee-jerks were not obtained, and in the lower limbs extension at the knees was much impaired, being almost impossible on the left side. Adduction and flexion of the extended legs on the pelvis were also weak, the right being weaker than the left. He could sit up in bed without the aid of his arms, but could not do so against the least resistance. If, when standing, he inclined forward off the perpendicular he collapsed and grasped his ankles. He rose from the recumbent to the erect position and walked in the manner characteristic of his affection. He could just manage to climb stairs without assistance, but always with the left foot leading. In the arms, extension at the elbow was weak, and movements of the supraspinati, and serrati were minimal. Adduction was performed only by the clavicular part of the pectorales.

Glycine was commenced nine days after admission, and during his four months' residence in hospital he gained 2.4 kg. and felt generally stronger. He was not aware of any improvement as regards his specific weakness, except that he found it easier to lift his feet when walking. Objectively there was increased power in extending the legs at the knee and in sitting up in bed against resistance. There was no improvement on rising from the ground or climbing stairs.

*Case 5. 56.6 kg.*

	No. of days.	Average daily excretion.		Remarks.
		Creatinine N. mg.	Creatine N. mg.	
Basal diet	3	159	52	
Basal diet + 4.4 grm. creatine	1	197	437	59 % creatine retained
Basal diet	1	203	146	(first 3 days)
" "	1	231	156	
Basal diet + 15 grm. glycine	10	158	112	Maximum creatinuria
Basal diet	16	—	—	(N.) 175 mg. noted on
Basal diet + 15 grm. glycine	5	—	—	5th day following
Basal diet	3	—	—	glycine. Basal value
Ordinary diet + 15 grm. glycine	12	—	—	had not been reached
Basal diet	6	—	—	before glycine was
" "	3	293	65	given
Basal diet + 4.4 grm. creatine	1	479	698	45 % creatine retained
Basal diet	1	312	140	(first 3 days)
" "	1	269	145	
Basal diet + 15 grm. glycine	7	238	143	Maximum creatinuria
Ordinary diet + 15 grm. glycine	24	—	—	(N.) 204 mg. noted on 1st day following glycine

*Case 6. Pseudo-hypertrophic muscular dystrophy.*

W. B., Male, aged 11, complained of difficulty in walking for five years, and in rising from recumbency or from a chair.

He was the seventeenth child in a family of twenty-one, the third child of his father's third wife. No history of any familial dystrophy could be obtained.

On admission he could not walk, and could only stand if supported. On

attempting to rise from the recumbent position he could get no further than on to his hands and knees. He could not sit up in bed without assistance. The arms were weak. The triceps jerks and the left knee-jerk were absent and the right knee-jerk was very sluggish. At first he was afraid to try to walk, but later could walk about fifteen yards with the aid of a guiding hand. Glycine was then commenced. This patient was the most unreliable patient in the series, as he sulked and had fits of temper during which he would not walk for a day or two.

He was five months in hospital and gained over 4.4 kg. in weight, became less anaemic and generally stronger. He regained some power in flexing his knees, could walk without assistance and even carry some dishes, and was able to sit up in bed without aid. He could climb eight steps of the stairs, and his time for a test distance thereon, as well as on the level, improved. He could rise from bed without assistance and put on some of his clothes. On the other hand, he showed no improvement in rising from the floor, and only a little in his arm movements. The condition of the reflexes remained unchanged. Eight months after discharge from hospital he was unable to return to report, as he had steadily deteriorated and was unable to walk.

*Case 6. 24.9 kg.*

	No. of days.	Average daily excretion.		Remarks.
		Creatinine N. mg.	Creatine N. mg.	
Basal diet	5	21	99	78 % creatine retained (first 3 days)
Basal diet + 2.64 grm. creatine	1	16	174	
Basal diet	1	18	159	
" "	1	13	153	
" "	1	12	93	
Basal diet + 10 grm. glycine	4	115		Creatinine could no longer be accurately determined as very low. Values expressed as total creatinine (including creatine).
" "	4	153		
" "	4	99		
" "	4	188		
" "	4	238		
Ordinary diet + 10 grm. glycine	26	—		Maximum value observed 308 mg. on 16th day following glycine
Ordinary diet	16	—		
Basal diet	2	43	60	
Basal diet + 2.64 grm. creatine	1	53	639	30 % creatine retained (first day)
Basal diet	1	51	116	
" "	1	44	78	
" "	19	51	76	
Basal diet + 10 grm. glycine	4	40	83	Maximum creatinuria (N.) 170 mg. noted on 8th day following glycine
" "	4	45	128	
Basal diet	2	—	—	
Basal diet + 10 grm. glycine	9	—	—	
Basal diet	11	49	113	
Basal diet + 10 grm. glycine	4*	55	123	Maximum creatinuria (N.) 171 mg. noted on first day following glycine
" "	5*	44	111	
" "	5*	47	102	
" "	6*	—	—	

*Case 7. Pseudo-hypertrophic muscular dystrophy.*

M. G., Male, aged 12, admitted, complaining of difficulty in ascending stairs and of a rocking gait for a year.

At the age of eleven he had been referred to the school doctor because of difficulty in keeping step during drill. No history of familial dystrophy could be obtained. On attempting to rise from the floor he could get no further than on to the hands, right toes, and left knee. He was unable to sit up without using his arms. When prone he could raise the right leg four inches off the bed and the left one inch. Movements at the shoulders were much impaired, and movements at the elbows were also weak. He had a typical gait and could only ascend stairs with the arms supporting him against the wall on his left side; he could descend with the assistance of the stair rail.

After over three months' treatment with glycine he was generally stronger and had gained 2.2 kg., but as regards the specific muscles affected by the disease there was practically no change in power. He could not sit up in bed unaided and could rise no better from the floor.

Seven months after discharge from hospital he was unable to return to report as he could only walk when supported by two people, and then only for a very short distance. He could not ascend stairs at all, and generally was much weaker.

*Case 7. 35.4 kg.*

	No. of days.	Average daily excretion.		Remarks.
		Creatinine N. mg.	Creatine N. mg.	
Basal diet	4	56	31	
Basal diet + 2.64 grm. anhydrous creatine	1	48	319	64 % creatine retained (first two days)
Basal diet	1	53	56	
" "	1	49	43	
" "	1	52	48	
" "	27	60	34	
Basal diet + 10 grm. glycine	8	54	86	Maximum creatinuria (N.) 151 mg. noted on 2nd day following glycine
Basal diet	8	—	—	
Ordinary diet + 10 grm. glycine	5	—	—	
Basal diet + 10 grm. glycine	3	85	63	Maximum creatinuria (N.) 354 mg. noted on 8th day following glycine
" "	4*	71	196	
" "	4*	58	158	
" "	4*	65	130	
" "	5*	67	130	
" "	4*	—	—	

*Case 8. Pseudo-hypertrophic dystrophy.*

A. B., Male, aged 10, when admitted on 3.6.32, could not rise from the floor without the assistance of his hands above his knees. Movements at the elbow and shoulders were very weak. The lower pectorals were atrophied and the latissimus dorsi muscles were inactive, while the rhomboids and spinati were very weak. The right knee-jerk was almost absent and the supinator and triceps jerks were absent on both sides. He walked with a rocking gait and could only climb a flight of stairs with the left foot leading and by pushing off the left thigh with his arm. No familial history was obtained. He had a right otorrhoea, and for this a mastoid operation was performed on 27.4.33. Glycine was commenced on 18.6.32. He was in hospital over three months and showed very striking general improvement.

He was able to rise from the ground with only the slight assistance of the left hand placed above the left knee, and power was regained in flexing the right leg on the trunk and in movement at the elbows. He became steadier on his feet and could climb stairs without the aid of his hand on his knee. When glycine was discontinued for ten days during his treatment he regressed, requiring again the aid of both hands above his knees to get up, and losing the improvement gained in movements at the right hip and the elbows. After a further five weeks on glycine he regained no more power than he did after his first course. He gained during his residence 2.6 kg., was generally stronger, but no other improvement was noted in the affected muscles or in the reflexes.

*Case 8. 20.4 kg.*

	No. of days.	Average daily excretion.		Remarks.
		Creatinine N. mg.	Creatine N. mg.	
Basal diet	3	44	41	
Basal diet + 2.64 gm. anhydrous creatine	1	53	295	42 % creatine retained (first 3 days)
Basal diet	1	53	165	
" "	1	70	151	
" "	15	55	50	
Basal diet + 10 gm. glycine	4	115	62	Maximum creatinuria (N.) 86 mg. noted on 4th day following glycine
" "	3	84	68	
Basal diet	4	—	—	
Basal diet + 10 gm. glycine	12	—	—	
Basal diet	11	59	75	
Basal diet + 2.64 gm. creatine	1	83	607	21 % creatine retained (first 3 days)
Basal diet	1	70	161	
" "	1	67	118	
Basal diet + 10 gm. glycine	8	60	131	Maximum creatinuria (N.) 154 mg. noted on 1st day following glycine
Ordinary diet + 10 gm. glycine	23	—	—	

*Case 9. Muscular dystrophy.*

W. G., Male, aged 40 years, weight 66 kg., was admitted to this hospital under Dr. Harrington's care. He dated the onset of his infirmity to an excessive amount of painting work undertaken two years before—work which he was not used to performing normally. For several months he had massage and electrical treatment, but without noticeable effect on his musculature.

On admission he was unable to brush his hair, unable to touch the shoulders with the corresponding arm, and unable to hold his arms out horizontally, either laterally or in front. The posterior neck muscles were also weak.

After sixteen days treatment with glycine (7.5 gm. twice daily) he was able to brush his hair and could approximate his arms more nearly to the horizontal position. The patient was conscious of definite improvement in the power of his affected muscles. He was then dismissed.

When re-examined at fortnightly intervals over a period of four months, the patient having received glycine continuously, some further improvement was noted, and at the end of this period he could hold his arms in the horizontal position both laterally and in front, and was conscious of

increased power in these muscle movements and in those of the trunk. The improvement, however, was not striking. He had no other treatment whilst in hospital and was not confined to bed. Regression has now taken place despite continued therapy.

No urinary observations were made on this case.

*Case 10. Post-arthritic atrophy.*

R. C., Female, aged 12, had a selective muscular atrophy, suggestive of post-arthritic condition, but without any history of arthritis. She had, however, an enlarged left heart and a double murmur best heard at the aortic area. She had chorea at the age of 9 years.

	No. of days.	Average daily excretion.		Remarks.
		Creatinine N. mg.	Creatine N. mg.	
Basal diet	8	93	43	
Basal diet + 2.64 grm. anhydrous creatine	1	108	391	59 % creatine retained (first day)
Basal diet	1	80	41	
" "	1	88	41	
" "	4	100	26	
Basal diet + 10 grm. glycine	6	87	51	Maximum creatinuria (N.) 68 mg. noted on 5th day following glycine
" "	12	—	—	
Basal diet	3	110	39	
Basal diet + 2.64 grm. creatine	1	103	255	59 % creatine retained (first 3 days)
Basal diet	1	115	145	
" "	1	94	60	
Basal diet + 10 grm. glycine	10	102	49	Maximum creatinuria (N.) 82 mg. noted on 8th day following glycine
Ordinary diet + 10 grm. glycine	34	—	—	
Ordinary diet	20	—	—	
Ordinary diet + 10 grm. glycine	40	—	—	
Basal diet + 10 grm. glycine	4	121	68	
Basal diet	4	127	50	
Basal diet + 2.64 grm. creatine	1	164	316	62 % creatine retained (first 2 days)
Basal diet	1	128	94	
" "	1	132	58	
Basal diet + 10 grm. glycine	9	118	67	Maximum creatinuria (N.) 97 mg. noted on 7th day following glycine
" "	7	—	—	

The patient complained of a limp, of being easily tired on walking, and of weakness of the left arm. The right leg was 4.75 cm. shorter than the left, the left side of the pelvis was tilted upwards, and there was a compensatory lumbar scoliosis. Passive movement at the hips was unrestricted. There was considerable atrophy of the right leg and left upper arm, as well as of the gluteal muscles on the right side, with 8 cm. wasting in the thigh, 1.5 cm. in the calf, and 3 cm. in the upper arm compared with the opposite side. The lower pectoral and latissimus dorsi muscles on the left side were apparently absent. The triceps and supinator jerks were absent in both arms and the biceps jerks were sluggish. The right ankle and the right knee-jerks were absent. Flexion of the wrist, pronation, supination and flexion and extension at the elbow were all very weak on the left side. She could not raise the right leg from the bed, and extension of that knee was

very weak. She could rise normally from the floor, and there was no apparent weakness of the trunk muscles.

The patient was in hospital for six months and had glycine from 2nd May till 10th June, and from 27th June till 3rd September. Her general improvement was striking, and she gained 2.4 kg., but as she had come from a very poor home, part of this improvement might be ascribed to hospital hygiene and feeding.

There was no improvement in flexing the right leg on the trunk, or in extending the knee, but the right ankle jerk was obtained. In the left upper extremities the supinator jerk was regained and more power was noted in flexion of the wrist in pronation, and supination, and also slightly in flexion at the elbow. No deterioration was noted following the cessation of glycine during a period of seventeen days prior to dismissal.

*Case 11. Muscular atrophy of Charcot-Marie Tooth type.*

F. H., Female, aged 13, had suffered from increasing weakness in the legs since the age of four and a half years, and from weakness in the arms for two and a half years. There was no family history of any disease of the nervous system. The atrophy involved the upper as well as the lower extremities. The reflexes were normal in the upper extremities, but the patient could not separate her fingers or adduct the thumbs, while movement at the wrists, the grasp, and flexion of the fingers were weak. In the lower extremities the ankle-jerks and plantar responses were absent, and there was almost complete paralysis of the muscles below the knees, except for slight power of extension of the right foot. She was able to walk in surgical boots with supporting iron splints.

She was in hospital forty-two days, during twenty-three of which she received glycine. Although she seemed and felt generally stronger, no improvement was noted in the specific muscles affected. Increment in weight 0.9 kg.

*Case 11. 47.6 kg.*

	No. of days.	Average daily excretion.		Remarks.
		Creatin- ine N.mg.	Creatine N. mg.	
Basal diet	3	261	44	
Basal diet + 2.64 gm. creatine	1	252	502	44 % creatine retained
Basal diet	1	258	62	(first 2 days)
" "	1	236	34	
" "	1	227	54	
Basal diet + 10 gm. glycine	6	210	60	Maximum creatinuria
" "	6	201	58	(N.) 92 mg. noted
" "	6	191	79	on 14th day follow-
" "	5	107	95	ing glycine

*Summary of Experimental Results*

*Muscular dystrophies.* On the basal diets of comparable protein content, the creatinurias of the adults varied from 0.9 mg. (Case 5) to 2.3 mg. (Case 2) N. per kg. per day, that of the children from 0.9 mg. (Case 7) to 4.0 mg.

(Case 6) N. per kg. per day. The basal creatinurias of Milhorat's two best cases, 1 and 3 had daily excretions of only 0.2 and 0.1 mg. N. per kg.

The creatinurias coinciding with these creatine excretions varied in the adult group from 2.3 mg. (Case 2) to 5.1 mg. (Case 1) N. per kg. per day, and amongst the children from 0.8 mg. (Case 6) to 2.1 mg. (Case 8) N. per kg. per day.

TABLE II.

CASE	1	2	3	4	5	6	7	8	10	11
SEX	F	F	F	M	M	M	M	M	F	F
AGE	24	31	38	35	26	11	13	9½	12	13
WEIGHT ON ADMISSION KG.	41.3	47.4	37.5	67.9	56.6	24.9	35.4	20.4	24.3	47.6
ON DISMISSAL KG.	42.8	53.7	42.3	69.4	59.0	24.3	37.6	25.0	26.7	48.6
CREATINE COEFFICIENT	5.1	2.3	3.0	4.4	2.8	0.8	1.6	2.1	4.0	5.5
CREATINE TOLERANCE :										
PER CENT RETAINED { BEFORE GLYCINE	43	60	75	41	59	78	64	42	59	44
{ AFTER GLYCINE	41	49	82	71	45	30	—	21	62	—
CREATININE—CREATINE (AVERAGE DAILY EXCRETION DURING PRE-PERIOD AND DURING PERIOD OF MAXIMUM DAILY CREATINURIA, AS MG. CREATININE N.)										
TIME OF OCCURRENCE OF MAXIMUM DAILY CREATINURIA: AFTER GLYCINE	5 <sup>TH</sup> DAY	1 <sup>ST</sup> DAY	5 <sup>TH</sup> DAY	10 <sup>TH</sup> DAY	5 <sup>TH</sup> DAY	16 <sup>TH</sup> DAY	2 <sup>ND</sup> DAY	4 <sup>TH</sup> DAY	5 <sup>TH</sup> DAY	14 <sup>TH</sup> DAY
GLYCINE PER DAY X NUMBER OF DAYS FED.	15x51	15x88	15x88	15x71	15x57	10x83	10x84	10x40	10x52	10x23
DISEASE.	M.D.	M.D.	M.D.	P.H.M.D.	P.H.M.D.	P.H.M.D.	P.H.M.D.	P.H.M.D.	M.A.	C.M.T.

M.D. = MUSCULAR DYSTROPHY; P.H.M.D. = PSEUDO HYPERTROPHIC MUSCULAR DYSTROPHY.  
M.A. MUSCULAR ATROPHY; C.M.T. = CHARCOT MARIE TOOTH TYPE.

It may be generally stated that the greater the muscular incapacity the greater the degree of creatinuria and the less the excretion of creatinine. This is in agreement with Harris and Brand's (17) findings.

The creatinine excretion of Case 6 was remarkably low, being at times inestimable. He exhibited the greatest muscular incapacity of the series.

*Reaction to the ingestion of creatine.* 4.4 grm. anhydrous creatine were ingested in one dose by the adult cases, 2.64 grm. by the children.

It will be observed from Table I that normal adults can retain generally 73–84 per cent. of 4.4 grm. creatine ingested, but that the retention may fall as low as 47 per cent. The retention capacity of children is even more variable. In diseases involving the muscular system other than the dystrophies, the capacity to retain ingested creatine is very variable.

The doses of creatine used in this investigation have been perhaps too large, but they were selected in order to exceed the possible increased tolerance for this substance, since with smaller amounts Harris and Brand

(17) found that the extra creatinuria in cases of dystrophy might correspond to 40-120 per cent. of the amount fed. These authors do not discuss the fact that in three patients they obtained over 100 per cent. recovery. If the discrepancy is not due to errors in technique then it must be presumed that the ingestion of creatine is itself responsible for an increased stimulation of creatine excretion, and this occurrence might indicate that the extra creatinuria which results from glycine feeding may not be due to a conversion of part of it to creatine, but to some stimulating or irritative effect.

It will be noted that in the present series of cases of muscular dystrophy the initial retentions of ingested creatine varied from 41-60 per cent. of the intake in the adults and from 42-78 per cent. in the children. In the two cases of muscular atrophy the percentage retentions were 59 and 44.

Following glycine therapy a definite increased retention capacity for creatine was noted in only one case (Case 4). Four cases showed definitely diminished retention capacities. In three cases there was a definite coincident increase in the creatinine excretion. Cases 5 and 8 showed progressive rises. The rise in Case 5 was from 159 mg. N. to 231 mg. N., the maximum occurring on the third day following the ingestion of creatine. The rise in Case 8 was from 44 mg. N. to a maximum of 104 mg. N. on the fifth day. Harris and Brand (17) do not record any changes in the preformed creatinine excretion as the result of creatine feeding.

In a personal communication Professor Thomas has hinted that large doses of creatine may do harm. He is inclined to attribute our failure to note increased retentions following glycine therapy to this cause. On the other hand, Harris and Brand using considerably smaller quantities of creatine have also failed to note an increased retention capacity.

*Reaction to the ingestion of glycine.* It will be noted from Table I that Harris and Brand (17) failed to find any extra creatinuria following the feeding of 7.5 gm. glycine to normal subjects, and we have failed to note any change to occur as the result of feeding 12 gm. glycine to two children. In an adolescent normal female a slight increase in the creatinuria did result from glycine feeding, the maximum being noted on the second day of therapy. In a student undergoing training in massage and in an early case of disseminated sclerosis no extra creatinuria resulted from glycine feeding despite marked initial creatinurias. These cases were all on creatine and creatinine-free diets.

Zwarsen (39) has noted that the ingestion of glycine is without effect on the hourly excretion of preformed creatinine in man.

Following the ingestion of glycine the creatine excretions increased in all the cases of dystrophy, in some to three or four times their basal values. The maximum daily creatine excretions in the various cases did not always occur in the period of maximum excretion, though this was generally the case. These maximum periods of creatine excretion occurred during the first three weeks of therapy.

Following these periods of maximum excretion the daily excretions of creatine generally fell: in some to below the basal level. In Case 2 it rose again. The recommencement of glycine feeding after an intermission was generally accompanied by an increased creatinuria.

Reinhold *et al.* (28) noted that in their Cases 1 and 2 the extra creatine resulting from glycine therapy did not tend to decrease.

With the exception of Cases 1, 4, 5, and 8 of this series the administration of glycine had little if any effect on the preformed creatinine level. The creatinine output of Case 1 rose a little, while that of Case 4 slowly declined as the creatinine rose. Later the creatinine rose a little. The creatinine output of Case 5 rose steadily, reaching its maximum recorded value on the fifth day after the cessation of the glycine. It is of interest that it was this same case which demonstrated the greatest change in the creatinine excretion following the ingestion of creatine. It is uncertain how much of this change was due to the administration of glycine. The creatinine excretion of Case 8 tended to vary as the creatine output.

*Muscular atrophies.* While the initial daily creatinurias of these two cases were 2.0 and 0.9 mg. N. per kg. body weight,—values in no way different from the dystrophic group—the creatinine excretions were appreciably higher.

The exhibition of glycine caused a very slight rise in the creatine output of Case 10, the maximum being observed on the fifth day of therapy, and in Case 11 an immediate increment in the creatinuria resulted with a corresponding decline in the preformed creatinine. These raised levels were not sustained and soon fell to the pre-glycine values. In Case 10 there was a subsequent slight rise on renewal of the glycine administration. In Case 11 following the first decline in the creatinuria, there occurred a secondary rise to a higher level than the initial value.

In myasthenia gravis, periodic familial paralysis, and in Charcot-Marie Tooth type of muscular atrophy, Harris and Brand (17) observed slight but definite increments in the creatine excretion on giving glycine. Milhorat (26) noted a slight extra creatinuria in a case of spastic spinal paralysis with muscular atrophy.

### Discussion

These experiments confirm the original observation of Brand and his collaborators (8) on the capacity of ingested glycine to increase temporarily the amount of urinary creatine excreted by cases of muscular dystrophy. From the biochemical standpoint it is also evident that while these observations substantiate the general findings of Thomas and his co-workers, one or two points of difference exist.

The tendency for an inverse relationship between the excretion of creatine and creatinine, which was noted by the Leipzig school, has been

observed in only two of our cases. Neither did the rate of creatinine excretion remain constantly unchanged, as Harris and Brand (17) noted in their comparable series of cases. In one of our series the creatinine output varied with the degree of creatinuria. No explanation is offered to account for these variations. Probably 'Weil es sicher sehr viele Ursachen innerhalb und ausserhalb des Muskels für die Bildung von Kreatinin gibt und wir ja im Harn nur den statistischen Querschnitt aus allen diesen Prozessen erfassen' (Thomas).

The metabolic differences in the reaction of the dystrophic and atrophic groups of our patients to ingested glycine appear to be of quantity rather than quality—an observation somewhat at variance with the conclusion reached by Thomas and his collaborators as a result of their observations. This quantitative difference, however, is in agreement with the observations of Harris and Brand, who also found a slight rise to occur in certain neuromuscular conditions as a result of glycine administration.

Like Harris and Brand we have been unable to confirm the increased capacity to retain ingested creatine which Thomas, Milhorat, and Techner (35) originally noted to result from glycine therapy. The data presented in a subsequent paper by Milhorat (27) indicate that this increased tolerance, developed as a result of glycine therapy, was only observed in one case. Sufficient data relative to this question are not provided in Milhorat's last paper, so that no generalization can be made from his figures.

Only one of our cases exhibited an increased capacity to retain creatine. The remaining cases of dystrophy, in which a second tolerance test was made, showed a diminished ability to hold creatine.

Thomas, Milhorat, and Techner (36) have found that, in addition to glycine,  $\gamma$ -amino butyric acid also raises the creatine output in dystrophy cases. Clinical experiments with this compound have not so far been made, but they have found that this amino acid does not produce the same rise in the output of urinary creatine, as does the corresponding amount of glycine fed to the same patient. Thomas and his collaborators have rejected the view that arginine is the direct source of creatine. They believe in a 'Neubildung des Kreatin und nicht mehr an die unmittelbare Herkunft aus Arginin', and consider that only at the commencement of the glycine therapy, and only in part, is this latter substance changed to creatine. Kostakow and Slauck (22) agree with this statement. Hunter (18) has suggested the possibility that the mother substance of creatine may be the 'still-combined arginine of the muscle or other protein'. On the other hand, Rose (30) considers that 'the possibility of creatine formation from some precursor through arginine as an intermediate' has not yet been excluded. Speculation is futile without further experimental data.

From the clinical standpoint all our cases with muscular dystrophy and the two cases of muscular atrophy also treated with glycine showed some general improvement. All gained in weight, and, apart from the long-standing pseudo-hypertrophic Cases 4 and 5, their general appearance was

improved. In all except Case 4, who was subject to attacks of depression throughout, a feeling of well-being was experienced, and generally power was regained. Locomotion and other movements, not specifically affected by the disease, were carried out more easily without the sensation of fatigue on slight effort which all had experienced before. In our opinion this general improvement is in excess of that which might have been expected from rest in bed and hospital hygiene, even though some of our patients came from very poor homes. We consider that such improvement as occurred was, in part, due to metabolic changes induced by glycine.

We also consider that there has been some improvement in the power of some of the specific muscles affected. This was least apparent in the pseudo-hypertrophic group. In no sense of the word can the term 'cure' be applied to the end results, as none of our patients who had previously been unable to rise from the floor or sit up in bed or ascend stairs unaided prior to glycine administration, could perform these actions after treatment. In the pseudo-hypertrophic group only Case 8 showed really definite specific muscular improvement. The slight localized improvement shown by the others in this group was difficult to separate from that consequent on the general gain in strength. Case 4 exhibited no improvement in the affected muscles.

The patients were asked to note if they experienced any unusual sensations in their muscles—three did so. The only sensation directly referable to the administration of glycine was the 'tingling' felt by Case 9 seven minutes after its ingestion.

General and local regression appeared to occur after the administration of glycine was stopped. This often coincided with dismissal from hospital. For this regression a psychic factor may be responsible, as these patients returned home with the hope of cure unfulfilled, and in most cases to an environment less equable than hospital life. Case 9, whose illness was of comparatively recent onset, noted slight further improvement when undergoing glycine treatment at home. Regression subsequently occurred despite continued therapy. Case 1 was kept in hospital for eight weeks after the discontinuance of glycine, during her second admission, regression did not, however, occur. This fact was the more striking when contrasted with the rapid regression which occurred as the result of returning to work when dismissed from hospital following her first period of glycine therapy.

It is extremely difficult, if not impossible, to determine how much of the improvement in the specifically affected muscles of these cases was due to increased activity of the healthy fibres, and how much was due to renewed functions of those affected fibres not yet completely atrophied. Thomas, in a personal communication, states that the lack of striking specific improvement in some cases of muscular dystrophy, particularly those of long duration, may be attributed to the fact that in these cases there are present in the affected muscles only atrophied and normal fibres. He believes that the action of glycine is particularly related to those fibres which are affected by

the dystrophy but not yet functionless. Milhorat (27) and Reinhold *et al.* (28) support this argument by sections of muscle obtained by biopsy.

In our two cases of muscular atrophy, also treated with glycine, general improvement occurred. There was also an increased sensation of well-being. In Case 10 some power was regained in certain of the affected muscles.

From a survey of the literature and from our own experience it is apparent that some cases of muscular dystrophy have reacted specifically and with much benefit to the exhibition of glycine, others have shown little or no specific improvement. It is difficult to account for these differences in clinical experience. For the present we can only record our observations.

### *Summary*

1. Nine cases of muscular dystrophy, five being of the pseudo-hypertrophic type, and two cases exhibiting selective muscular atrophy, have been investigated in relation to their response to ingested glycine.

2. In the pre-glycine period it was noted that in general the greater the muscular incapacity the greater the degree of creatinuria.

3. All the cases showed a temporarily increased creatinuria as the result of glycine administration, the atrophic cases exhibiting the least response.

4. Following the period of maximum creatinuria the daily excretion generally fell; in half the dystrophic cases to below the pre-glycine level.

5. With one exception the cases belonging to the dystrophy group showed definite general improvement as evidenced by increase in weight, general gain in strength, and feeling of well-being. None became worse.

6. In the majority there was also some evidence of improvement in the power of some of the specific muscles affected, but this was least in the pseudo-hypertrophic group.

7. Some general improvement was noted in the two cases of muscular atrophy. One showed some increase in power of the affected muscles.

8. We believe that in the majority of these cases the changes were in excess of those which might be expected to occur from hospitalization alone, but that the term 'cure' cannot be applied to the end results.

Prof. Karl Thomas has kindly read this paper, and in his reply furnishes further particulars of their cases (Milhorat (36)).

Case 1, their best case, had pulmonary tuberculosis in addition to his muscular dystrophy. It appears that despite this and the marked loss of weight, the patient's muscular capacity did not decline so long as he had glycine. When glycine was stopped rapid regression took place. Cases 2 and 7 became worse, ephedrine being without action on Case 2. The condition of Cases 3, 5, 8, and 9 remained unchanged.

Prof. Thomas now considers that the nature and also the course of progressive muscular dystrophy is such that glycine causes but little improvement in the majority of cases, and in spite of administration the disease may advance in some cases. In particular is this true in the case of pseudo-hypertrophic muscular dystrophy and also those cases in whom the dystrophy begins in early life.

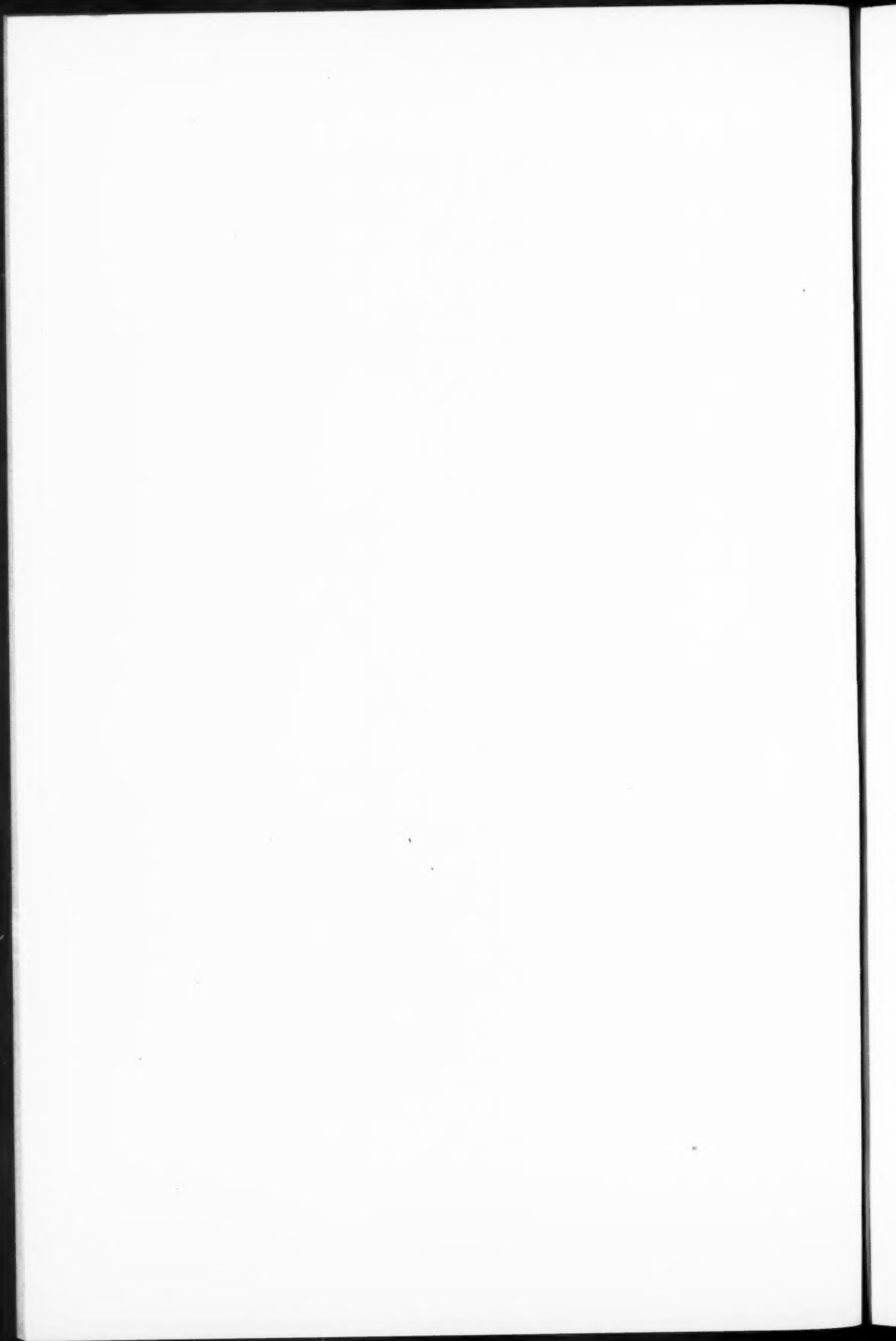
In conclusion, we wish to express our gratitude to those members of the Staff of the Glasgow Royal Infirmary, in particular Dr. A. Muir Crawford, who allowed us to include some of their cases in this investigation.

Our thanks are also due to Sister Cumming for her unremitting care in the course of these experiments.

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## PROLONGED RESIDENCE IN HIGH OXYGEN ATMOSPHERES<sup>1</sup>

### EFFECTS ON NORMAL INDIVIDUALS AND ON PATIENTS WITH CHRONIC CARDIAC AND PULMONARY INSUFFICIENCY

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IN previous communications (1) we described some of the effects produced in patients with advanced heart failure, by prolonged residence in atmospheres containing 40 to 50 per cent. oxygen. The investigation has been continued and now includes studies on twenty-eight patients with various forms of chronic cardiac and pulmonary disease, treated in this manner; and on two normal individuals. We have extended the scope of the work, and have been able to define more clearly the particular types of response that occur in certain different forms of these conditions. These observations form the basis of the present paper.

#### I. *Recent Literature*

An extensive review of the early literature on oxygen therapy was written by Pagel in Michaeli's *Handbuch der Sauerstoff-therapie* (2), published in 1906. A general article by Boothby (3) (1932) contains references to much of the modern work on the subject. We shall refer here to only a few of the recent investigations, whose results bear directly upon the subject of the present study, namely, oxygen therapy in chronic cardiac and chronic pulmonary disease.

In 1927 Campbell and Poulton (4) reported the results of several years' work on the effects of continuous residence in an oxygen chamber upon subjects with dyspnoea. There was one case of myocardial failure (arteriosclerotic heart); several had cardiac failure secondary to chronic bronchitis or emphysema. Following residence in 40 per cent. oxygen, most cases improved, as evidenced by less dyspnoea, less cough and sputum, increased appetite, gain in weight. Respiratory frequency and ventilation were decreased, CO<sub>2</sub> concentration in the expired air was greater. Improvement sometimes was transitory, sometimes persisted for months. It was noted

<sup>1</sup> Received November 15, 1933.

that the patients treated for three weeks showed more improvement than those treated for a week or less.

Levy and Barach (5) and Rizer (6) reported favourable effects following continuous oxygen therapy in cases of coronary thrombosis.

The present authors (1) studied eight cases of chronic heart failure of different types, treated continuously in 40 to 50 per cent. oxygen. Improvement occurred in six cases, maximum benefit being obtained only after two or three weeks of treatment. Other phenomena noted were: (1) increased arterial oxygen saturation; (2) increased arterial blood  $\text{CO}_2$  levels; (3) in three cases a delayed rise in urinary output, progressing to complete disappearance of oedema.

Katz, Hamburger, *et al.* (7) reported improvement in four out of six cases of heart disease treated in an oxygen chamber, but no diuresis that could be attributed to this treatment. In a series both of normal individuals and of patients with heart disease, studied by these authors, residence in the oxygen chamber resulted in: (1) a slowing of the pulse-rate; (2) decreased pulmonary ventilation; (3) slightly decreased vital capacity; (4) increased arterial oxygen saturation in most, but not all cases; (5) increased blood  $\text{CO}_2$ .

Uhlenbruck (8) in 1930 discovered that patients with chronic cardiac or pulmonary disease frequently had a temporarily increased oxygen intake when breathing pure oxygen, compared with their oxygen intake when breathing air. This increase might persist for twenty to thirty minutes, and might amount in all to several litres of oxygen. The phenomenon was termed the 'oxygen deficit'. The oxygen deficit has since been used extensively, especially by Knipping (9) and his co-workers, as a criterion by which to judge a patient's need for oxygen therapy.

## II. *Object of Study and Clinical Material Available*

The purpose of the present investigation was (1) to determine the effects of a week's residence in an atmosphere of 45 per cent. oxygen, upon the metabolism of two normal persons. (2) To study in cases of cardiac and of pulmonary failure, the progressive alterations in blood gases, in water and electrolyte balances, and in circulatory dynamics, that occur during the course of two weeks or more of residence in oxygen-enriched atmospheres. (3) To differentiate the types of cardiac failure that respond favourably to prolonged oxygen therapy, from those that respond poorly or not at all.

The clinical material which we have used is (1) two normal young men. (2) Twelve cases of arteriosclerotic heart disease. Ten of these had congestive failure, two had symptoms of coronary disease without passive congestion. None of these cases was complicated by chronic nephritis. (3) Nine cases of chronic rheumatic valvular disease, with congestive failure. (4) Two cases of congenital heart disease, one being coarctation of the aorta, the other the tetralogy of Fallot combined with a patent ductus arteriosus.

All these patients had advanced cardiac or pulmonary symptoms at the time when oxygen treatment was begun. With two exceptions, no patient was accepted for oxygen treatment unless other measures had first been tried without success, and unless the patient's course at the time was either stationary or downhill.

### III. *Methods*

The oxygen chamber, which was used in most of these studies, has been described by one of us elsewhere (10). The temperature in the chamber was kept at  $66 \pm 2$  degrees Centigrade, and the humidity about 40 per cent. With the earlier cases studied, the circulation of air was accomplished by thermal means only, and the  $\text{CO}_2$  removed by passage of the air over soda-lime trays. The  $\text{CO}_2$  in the air was kept between 0.4 and 1.0 per cent. In several later cases a more rapid circulation was maintained by a large motor and blower, and the  $\text{CO}_2$  concentration kept below 0.5 per cent.

The oxygen tent, which we used in some instances, has also been described by one of us (11). The temperature and humidity conditions, and the content of  $\text{CO}_2$  in the air, were similar to those in the oxygen room.

During their control periods in the wards, the patients received whatever treatment their condition indicated, including digitalis, sedatives, paracenteses, diuretics, phlebotomy, and oxygen by nasal catheter. They were in most cases on a 'cardiac' diet—small frequent feedings, low fluid intake, and low salt (2 grm. NaCl per day). When transfer to the oxygen room was made, treatment was in other respects maintained the same. An exception to this was made in one case (see Table VI), whose salt intake was reduced during the course of oxygen room treatment. Patients admitted to the oxygen chamber were kept in it continuously for the duration of the treatment. In the use of the oxygen tent, it was found that the patients could usually be removed from it for half an hour two or three times a day, which greatly facilitated nursing care.

Pulmonary ventilation and oxygen consumption were measured in some cases by collection of expired air in a Tissot spirometer or Douglas bag; in other cases by graphic registration on a Benedict-Roth apparatus. The latter probably involved certain quantitative errors, due to the high concentrations of oxygen breathed during tests, but the qualitative changes observed were the same by this as by the other technique.

All blood samples taken, except those for total serum electrolyte values, were drawn from the brachial artery. The blood was not necessarily taken with the patient under basal conditions, as the alterations in blood-gas values which we were dealing with were greater than any diurnal variations. For total serum electrolyte studies, the patient was under fasting conditions, and blood was taken from an arm vein, without stasis; except in the case of patient L. S., all of whose blood specimens were arterial.

Blood for  $\text{O}_2$  and  $\text{CO}_2$  determinations were drawn under oil, transferred

under oil to containers with small amounts of dried neutral potassium oxalate and sodium fluoride, enough to make final concentrations of about 0.2 per cent. Blood-gas values were determined by the Van Slyke-Neill manometric apparatus, and oxygenated  $\text{CO}_2$  dissociation curves by a technique slightly modified from that of Austin, Cullen, *et al.* (12). It may be noted that we oxygenate blood in room air; and that by 'oxygen capacity' we mean the volumes per cent. of oxygen, contained in the blood after equilibration with room air at  $37^\circ\text{C}$ . Hydrogen ion concentrations in arterial serum were calculated from the arterial  $\text{O}_2$  and  $\text{CO}_2$  dissociation curves, by the use of the line charts of Van Slyke and Sendroy (13).

Blood for serum electrolyte studies was drawn under oil, allowed to clot, centrifuged, and the serum then drawn off. Analyses were made of concentrations of total base, bicarbonate, chloride, protein, phosphate, calcium, potassium, glucose, creatinine, oxygen capacity, cell volume (by hematocrit), serum water. The methods of analysis were those described recently by Loeb, Atchley, Richards, Benedict, and Driscoll (14).

Venous pressures (in mm. of water) were taken with the patient at rest, in a semi-recumbent position, by the direct method of Moritz and Tabora (15), the zero level of venous pressure being taken as 50 mm. below the lower edge of the manubrium sterni. The semi-recumbent position (angle of  $40^\circ$ ) was used as standard, on account of the orthopnoea present in many instances. This involved certain inaccuracies (16); but our interest lay chiefly in the changes in venous pressure during oxygen therapy, rather than in absolute values. Practically, we have found that the differences in venous pressure level due to change from semi-recumbent to recumbent positions, are usually less than 15 mm.

In the studies of electrolyte and water balances, conducted on two normal individuals and on patient J. Sn., the management and technique employed were those recently described in detail by Loeb, Atchley, *et al.* (14). In brief, the patient was placed upon a measured diet, identical each day. When a group of daily diets was prepared and weighed out, one day's sample was reserved for analysis and later analysed for its electrolyte contents—total base, calcium, potassium (sodium and magnesium were determined by difference), chloride, phosphorus (as phosphate), total nitrogen. The diet in each case was worked out, during a pre-experimental period, so as to be large enough to maintain body weight. Fluid intake was strictly regulated and was the same each day.

All urine and stools were collected. Urine was analysed for volume, pH, titrable acidity, ammonia, total nitrogen, total base, potassium, calcium,  $\text{Na} + \text{Mg}$  (by difference), chloride, phosphate, and creatinine. In the congestive failure case, J. Sn., organic acids in the urine were also measured. As all urine specimens were acid, the bicarbonate content was negligible. Stools were analysed for water content, total base, K, Ca, P.  $\text{Na} + \text{Mg}$  was obtained, again, by difference.

This technique thus gave a fairly complete balance sheet of daily intake

and output of the individual studied, except for such losses as occurred through lungs, skin, and sputum.

The three electrolyte balance studies which we are reporting, two on normal individuals and one on a case of pulmonary and cardiac insufficiency, were carried out through the collaboration of Dr. Dana Atchley, Dr. Robert Loeb, and their technical staff; to all of whom the authors express their thanks and appreciation.

#### IV. *Effects of a Week's Residence in 45 per cent. Oxygen upon Two Normal Men.*

The subjects were 20 and 23 years of age respectively, who came into the hospital as volunteers for the purpose, and received remuneration. Both were on a maintenance diet: one, subject N.P., on 184 gm. carbohydrate, 80 gm. protein, and 140 gm. fat; and the other, subject H.P., on 237 gm. carbohydrate, 76 gm. protein, and 124 gm. fat. The chief difference in the dietary regimes was in NaCl intake, N.P. receiving high salt intake of 10 gm. a day, and H.P. low intake of 1.9 gm. a day. They were kept on a regulated amount of activity each day, being allowed up in a chair four hours a day, and spending the rest of the day in bed. Fluid intake was 2,100 c.c. per day, in each case.

Water and electrolyte balances were studied as described under *Methods*. In addition, measurements were made of metabolic rate (Tissot apparatus), pulmonary ventilation, alveolar air, and cardiac output (method employing the Fick principle (12b)). Arterial oxygen saturation was determined in one case, and the oxygenated whole blood CO<sub>2</sub> dissociation curve in both cases.

Wet and dry bulb thermometer readings were taken during both control and oxygen room periods, and the oxygen room temperature and humidity regulated so as to be as far as possible the same, on the average, as they had been on the ward.

Control observations were carried out during the first ten days after the subjects had become stabilized on the above régime.

The various observations were repeated during the week's residence in the 45 per cent. oxygen atmosphere of the chamber.

Most of the functions measured were not appreciably altered during the week in the oxygen room (Table I).

Basal metabolic rate (measured by CO<sub>2</sub> output) was unchanged. This is consistent with the observations of Benedict and Higgins (17), and of Campbell (18).

Resting ventilation was not decreased, in fact it increased slightly. This may perhaps have been associated with the presence of CO<sub>2</sub> in the chamber air, in concentrations of 0.23 per cent. up to 0.77 per cent. Katz, *et al.* (7) found decreased ventilation by normal individuals when living in high oxygen, as noted above.

There occurred a rather striking fall in pulse-rate, of about ten beats per minute, in both cases, while they were in 45 per cent. oxygen. Katz, *et al.* (7), noted sinus bradycardia in their oxygen-treated individuals.

TABLE I

*Normal Subjects. Circulatory and Respiratory Measurements in Normal Atmospheric Air, and in 45 per cent. Oxygen*

Subject.	Date.	Venous oxygen saturation.	Oxygen capacity vols. %.	Arterial oxygen saturation.	Pulmonary ventilation.	CO <sub>2</sub> output.	O <sub>2</sub> absorbed.	Cardiac output.
N. P.	Room air	%	%	%	litres/min.	c.c./min.	c.c./min.	litres/min.
	24 Oct.	66	21.7	—	—	—	—	—
	28 Oct.	—	—	—	5.44	167	205	4.3
	29 Oct.	52	20.1	—	—	—	—	—
	30 Oct.	—	—	—	5.54	166	200	4.0
	31 Oct.	65	20.8	—	—	—	—	—
	11 Nov.	70	19.5	—	—	—	—	—
	13 Nov.	—	19.6	96	5.83	175	209	3.9
	45 % oxygen							
	18 Nov.	—	—	—	5.95	177	—	4.4
	19 Nov.	—	20.0	99	5.53	181	—	4.5
	20 Nov.	41	20.4	—	—	—	—	—
H. P.	Room air							
	1 Dec.	62	22.5	—	—	—	—	—
	9 Dec.	51	21.3	—	—	—	—	—
	10 Dec.	—	—	—	5.33	171	215	4.7
	14 Dec.	67	20.8	—	—	—	—	—
	16 Dec.	—	—	—	5.15	166	203	4.5
	45 % oxygen							
	21 Dec.	74	20.5	—	—	—	—	—
	22 Dec.	—	—	—	5.77	182	—	4.9
	23 Dec.	75	20.3	—	—	—	—	—
	24 Dec.	—	—	—	6.02	178	—	4.5

In both subjects, oxygen capacity of the blood decreased gradually during their stay in the hospital. This we have observed on other occasions, when normal individuals, previously ambulatory, remain for several weeks confined to bed. There was no appreciable acceleration in this gradual process during the week in the oxygen chamber.

In the one case measured (N.P.), the arterial oxygen saturation increased from 96 to 99 per cent.

Arterial blood-pressure showed no consistent changes in high oxygen.

The values of cardiac output, in the two cases, varied little in the oxygen room as compared with the values in the ward.

From the two facts just stated—small increase in arterial oxygen saturation and constant cardiac output—and upon the assumption that tissue oxygen tensions vary approximately as do the tensions in the venous blood, it can be deduced that the mean tissue oxygen tension at rest does not

change greatly as a result of the high oxygen atmosphere. A three per cent. increase in arterial oxygen saturation means an increase of about 20 mm. in tension, but in the middle part of the dissociation curve, where mean venous blood, under conditions of rest, is usually located, a three per cent. change in oxygen content is associated with less than 5 mm. change in tension. It should be noted that we are discussing here, in 'mean venous tension', a somewhat hypothetical value, since most tensions in local vessels are probably greater or less than this level. It should be further pointed out, therefore, that the effect of oxygen-enriched atmospheres upon the oxygen tension in the capillaries of a tissue, will depend upon the rate of blood-flow through that tissue, being greater, the greater the rate of local blood-flow. This follows directly from the form of the oxygen dissociation curve.

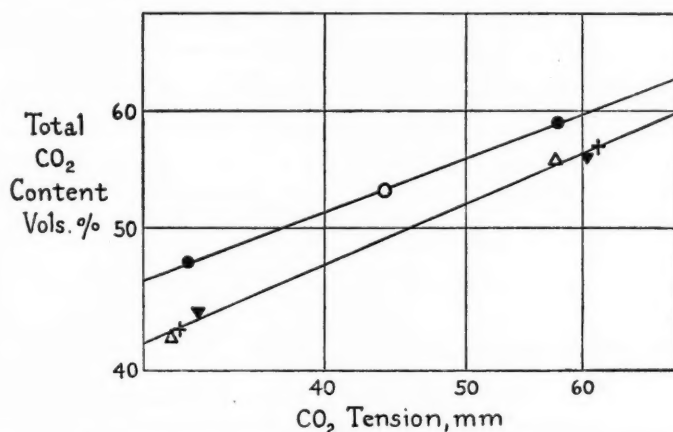


CHART 1. CO<sub>2</sub> dissociation curves of normal subject H.P. Lower curve, while patient was in room air. Upper curve, while patient was in 45 per cent. oxygen. A separate symbol is used for each day's determinations. Points are plotted logarithmically, so as to give the curves a linear form.

In animals, living for a number of days in 50 to 80 per cent. oxygen, Campbell (18) found increases in intra-abdominal oxygen tensions from 7 mm. in cats, up to 20 mm. and more in small monkeys.

From his observations on normal individuals, breathing 50 to 55 per cent. oxygen for two hours, Kroetz (19) deduced both a large increase in volume flow of blood, and a large increase in tissue oxygen tensions.

There was a small but definite rise in level of the CO<sub>2</sub> dissociation curve of whole blood, in both subjects, more marked with H.P. (Chart 1). This finding was recently reported by Katz, *et al.* (7). There were inconstant alterations in pH of the venous serum, due in part to differences in oxygen saturation.

In the electrolyte balances, there were a few minor changes during the week in 45 per cent. oxygen (Table II). The subject (N.P.), receiving high salt intake, had a decrease in serum chloride, approximately equivalent to

TABLE II

*Normal Subjects. Serum Electrolyte Values and Urinary Output, in Room Air, and in 45 per cent. Oxygen*

Subject.	Period.	Serum.				Body weight.	Urine output, average per day.				
		Tot. B. mol. equiv.	B-A mol. equiv.	Pro. mol. equiv.	HCO <sub>3</sub> mol. equiv.	Cl. mol. equiv.	Vol. c.c.	K. mol. equiv.	Na+Mg. mol. equiv.	Cl. mol. equiv.	N. grms.
N.P. High salt diet	I. Control 5 days	150.0	2.4	16.1	27.9	101.1	1,747	69.1	154.2	153.4	12.5
	II. Control 5 days	147.2	0.8	14.9	26.9	102.3	1,935	68.2	168.1	168.4	13.0
	III. Oxygen room 6 days	152.0	3.2	17.1	29.8	99.6	2,069	76.0	185.2	186.3	13.5
H.P. Low salt diet	I. Control 5 days	150.7	3.2	16.0	27.7	101.0	1,343	62.7	21.1	17.9	—
	II. Control 5 days	151.3	3.0	16.0	28.6	101.3	1,613	59.8	17.1	19.1	—
	III. Oxygen room 7 days	149.8	0.8	15.3	29.1	102.3	1,714	66.4	13.2	18.2	—

the rise in bicarbonate ; he had also a slight increase in urinary chloride and sodium output, but no significant change in urine volume. Subject H.P., on low salt intake, had only slight changes in serum chloride and in bicarbonate ; he had, furthermore, no significant change in chloride output, nor in urine volume. The other blood, stool, and urine electrolyte values, not given in Table II, showed no important changes.

Summarizing, one may say that two normal individuals, after residing for a week in an atmosphere of 45 per cent. oxygen, showed a considerable fall in pulse-rate, a small increase in arterial oxygen saturation (one case), and in the level of the  $\text{CO}_2$  dissociation curve. There were also a few alterations in sodium and chloride balance, minimal in extent, in one case.

#### V. *Effects of Residence in 45 per cent. Oxygen upon a Typical Case of Congestive Failure*

From our earlier observations (1) on the problem, it appeared, not only that there was a group of phenomena that took place when a patient with cardiac insufficiency responded favourably in an atmosphere of 45 per cent. oxygen, but that there was a sequence of events.

In several cases of the present series, a more detailed study has been carried out, with particular reference to the time relations of the phenomena noted.

In order to make the description concrete, we will give in some detail our observations on one of these cases, an American of 56 with arteriosclerotic heart disease and congestive failure.

L. S., No. 267189, admitted 30th August 1930. The patient was an American choir singer, 56 years old, who had had dyspnoea on exertion for a year, and for the three months preceding admission, orthopnoea, paroxysmal dyspnoea, cough, bloody sputum, and progressive swelling of the legs.

Physical examination on admission showed a large-framed, pale, middle-aged man, cyanotic, with laboured Cheyne-Stokes respirations. He coughed frequently, bringing up small amounts of bloody sputum. The heart was generally enlarged, transverse diameter 20.4 cm., the sounds were poor in quality, with gallop rhythm. There were moist râles at both bases, some dullness at right base. The pulse was alternating, blood-pressure 158/112. The abdomen was obese and tense, with shifting dullness and fluid thrill. The liver and spleen could not be felt. There was massive oedema over the sacrum and in the legs and scrotum. His temperature was  $101^\circ$ , pulse-rate 100, and respirations 28. The blood count was normal, the urine showed a trace of albumin and a few WBC. Blood urea was 0.45 gm./l. Blood Wassermann was negative.

Phlebotomy, sedatives, and other emergency measures administered on admission improved his condition slightly. Digitalis was given, but his tolerance for this drug was small. On his fifth day in the hospital, an injection of salyrgan brought a large diuresis of 4,000 c.c. In general, however, the patient's course during his eight days in the ward was unfavourable. Fluid accumulated in his right chest, urinary output was small, paroxysmal

TABLE III  
Patient L. S. Blood Electrolyte Values

Date.	Arterial whole blood.						Arterial serum.						Nonprotein nitro- gen mg./100.	8.9 p.m., into oxygen room	
	Venous P. mm. H <sub>2</sub> O.	O <sub>2</sub> cont. vols. %.	O <sub>2</sub> cap. vols. %.	Sat. %.	CO <sub>2</sub> cont. mol. equiv. %	pCO <sub>2</sub> mm.	Lact. acid mg./100.	T.B. mol. equiv.	Pro. %.	Pro. mol. equiv.	HCO <sub>3</sub> mol. equiv.	Cl. mol. equiv.			K. mg./100.
7.9.30	190	16.6	19.7	84	19.9	32	12.5	151.3	5.83	13.8	23.4	103.2	18.5	7.48	35
8.9.30	190	15.0	17.5	86	20.2	—	—	147.8	5.73	13.5	25.2	97.2	15.1	7.47	—
9.9.30	140	17.3	18.0	96	22.1	36	10.1	—	5.64	13.3	—	—	—	—	—
10.9.30	130	17.9	18.1	99	22.6	—	—	—	5.71	13.5	—	—	—	—	—
11.9.30	150	17.6	18.0	98	23.7	—	—	—	—	—	—	—	—	—	—
13.9.30	130	17.1	17.5	98	24.5	40	7.0	146.0	5.66	13.4	27.9	98.4	—	7.47	—
19.9.30	—	17.9	17.9	100	22.8	36	12.9	148.3	6.10	14.4	26.4	98.1	—	7.49	—
30.9.30	—	19.1	20.0	95	20.6	32.6	—	145.3	6.79	16.0	24.3	100.8	—	7.51	—

dyspnoea attacks were worse, with laboured Cheyne-Stokes breathing in the intervals between them. He became irrational and extremely restless.

On 7th September, at the end of his first week in the hospital, an arterial blood sample (Chart 2 and Table III) showed the oxygen saturation to be down to 84 per cent. Whole blood  $\text{CO}_2$  content was 19.8 mol. equiv.; and

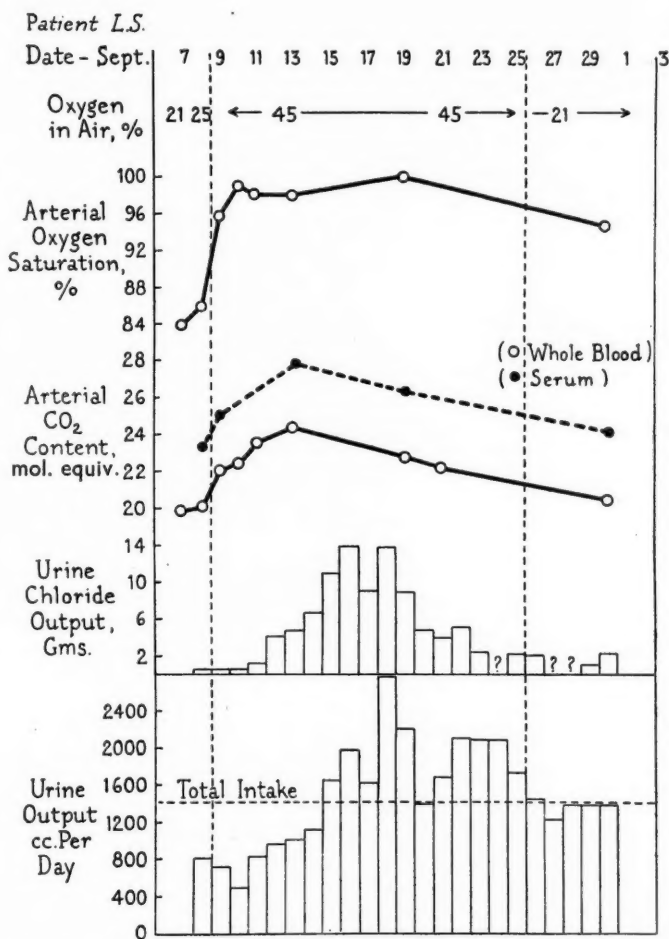


CHART 2. Response of blood gases and of urine output of patient L. S., during treatment in high oxygen.

serum pH 7.48. Arterial  $\text{CO}_2$  tension was 32 mm. Pulmonary ventilation could not be measured.

He had a poor night, and the next morning his condition was critical. Oxygen was given by nasal catheter with but slight effect. Arterial oxygen saturation was 87 per cent., and whole blood  $\text{CO}_2$  also little changed from the previous day's level.

As shown in Table III and in Chart 2, total base concentration in the

arterial serum was 151.3 mol. equiv.; protein 5.83 per cent.; chloride 103.2 mol. equiv.; and whole blood lactic acid 19.5 mg./100 c.c.

Venous pressure 180 to 200 mm.

The output of chloride in the urine at this time was at an extremely low level, that of sulphate somewhat elevated.

That afternoon, 8th September, he was transferred to the oxygen room, and the oxygen in the room raised rapidly to 42 per cent. Clinically, effects began to be noted during the course of the afternoon. The most definite was in his respiration, which became shallower and less laboured, though Cheyne-Stokes rhythm persisted. The patient's condition again precluded any measurement of pulmonary ventilation. There was an appreciable, though not marked, decrease in cyanosis. An important and early clinical phenomenon was the decrease in restlessness. Subjectively, the patient was less dyspnoeic, and less apprehensive.

The next morning his condition was about the same. His appetite was improved. Cyanosis was still quite marked. Physical examination generally showed little change. His blood-pressure, 135/95, was slightly lower. During the course of this day his temperature fell slightly, his pulse dropped to 93 from a previous average level of over 100. His respiratory rate, and the Cheyne-Stokes character of his respirations were unchanged.

The venous pressure was lower, 140 as compared with its previous level of 190.

Arterial blood, drawn on the morning of 9th September, showed a number of changes from the previous day (see Chart 2, and Table III). Oxygen saturation was now 97 per cent., the  $\text{CO}_2$  level of the blood had increased by about 2 mol. equiv., chloride was 3 mol. equiv. less, total base diminished to about the same extent. There was a slight fall in arterial serum pH. Serum protein was slightly lower.

During the next two days there was a little clinical improvement. Temperature and pulse-rate dropped further; pulsus alternans disappeared. The respirations were somewhat less rapid; the Cheyne-Stokes rhythm continued during the 10th, with very brief periods of apnoea; on the following day respirations became regular. Cyanosis decreased further, but did not disappear. Dullness at the right lung base increased: this was interpreted as increased chest fluid. Peripheral oedema appeared to be unchanged.

His arterial blood maintained its high oxygen saturation. There was a steady further rise in  $\text{CO}_2$  level. Total base and chloride of the serum were unfortunately not done again until 13th September; at this time chloride was practically the same as on 9th September, while total base was 2 mol. equiv. lower. Serum protein was unchanged.

During these first four days in the oxygen room urinary output remained low, considerably less than fluid intake, and chloride output less than 1 gm. per day.

On 12 September, an abrupt change occurred in urinary output, in that the chloride excretion suddenly increased to 4 gm., or 113 mol. equiv. There was perhaps a slight increase in urinary water output. Except for the chemical changes in his blood at this time, no other alteration in his condition was observed that might account for this increase. Arterial blood-pressure was at the same level, and venous pressure, 150 mm., the same as on his second day in the oxygen room.

Chart 2 and Table III show the progressive increase, first in urinary chloride excretion, and then in water output, that took place in the succeeding ten days. Clinically, a definite decrease in oedema was first noted on

15th September. On 23rd September physical examination showed no evidence of any oedema.

The arterial blood on 19th September, which was at the height of water diuresis, but after the crest of the chloride diuresis, showed a fall in  $\text{CO}_2$  content, no change in serum Cl, and perhaps a slight increase in serum total base. Venous pressure at this time was 130 mm., still above normal. Serum protein was definitely increased, for the first time since transfer to the oxygen room.

The clinical condition of the patient improved gradually but steadily. Orthopnoea disappeared by 21st September. Gallop rhythm of the heart persisted, but was less marked.

On 23rd September, two weeks after the patient's admission into the oxygen room, the oxygen in the air was reduced to 30 per cent. and maintained at this level for two days. The patient was then transferred back to the ward. For several days he had increased cyanosis, some dyspnoea, increase in gallop rhythm of his heart. These subsided gradually.

Arterial blood on 30th September was 96 per cent. saturated with oxygen,  $\text{CO}_2$  was back nearly to its level on 8th September before admission to the oxygen room. Arterial pH was a little increased. Serum chloride had increased slightly, total base was still well below the control period level, whereas there was a rise in oxygen capacity, and further rise in serum protein.

He was allowed up on 6th October, and sent home on 15th October 1930. He maintained compensation quite well until April 1931; was in the hospital for a week in May 1931; remained at home chronically decompensated through that summer, was finally taken to another hospital, where he died in September 1931.

From the above description, the progressive development of the recovery process, during the patient's two weeks in 45 per cent. oxygen, is evident. The sequence of events comprise four more or less distinct phases:

1. An initial period, lasting about a day, during which dyspnoea and restlessness were partly relieved, arterial oxygen saturation raised, arterial  $\text{CO}_2$  increased, venous pressure lowered (though still high).
2. A second period, of about three days, during which dyspnoea and orthopnoea were further relieved, though clinical changes were not marked, blood  $\text{CO}_2$  increased steadily, venous pressure remained the same.
3. The period of diuresis, lasting about nine days, during which water and salt output increased progressively to a maximum and then declined, clinical improvement continued and oedema disappeared, blood  $\text{CO}_2$  reached a maximum and then decreased slightly. Serum protein concentration increased during the course of diuresis.
4. The post-diuresis period, with improved heart action and disappearance of orthopnoea, with further decline in blood  $\text{CO}_2$ , and increase in oxygen capacity and serum protein.

Progress, generally similar to that just summarized, was followed by all the patients who showed decided improvement in high oxygen; though there were many differences in actual time intervals and other details.

TABLE IV  
Respiratory Functions—Changes following Oxygen Therapy

Patient.	Date.	Oxygen in air %.	Ventilation.		Respiratory rate.	Basal metabolic rate.		Vital capacity.		Clinical improve- ment.	Type of disease.
			litres per min.	per cent. change.		per cent. change.	li res.	per cent. change.			
A. L.	16.7.29	25	7.7	—	24	+5	—	—	—	—	Arteriosclerotic
	6.7.29	45	7.2	-6	25	+2	-3	—	—	Marked	
J. McQ.	16.8.29	21	11.8	—	25	+29	—	1.8	—	—	Arteriosclerotic
	22.8.29	45	7.5	-36	15	+17	-12	2.4	+15	Marked	
	30.8.29	45	6.2	-47	14	+4	-25	2.2	+12	—	—
J. Sn.	23.12.29	21	—	—	25	—	—	1.0	—	—	Pulmonary fibrosis
	28.12.29	21	11.7	—	32	202*	—	—	—	—	
	2.1.30	45	—	—	22	—	—	0.8	—	—	—
	6.1.30	45	10.3	-12	22	218*	+8	0.8	-20	Marked	—
I. S.	2.5.30	21	7.2	—	22	164*	—	1.4	—	—	Pulmonary tuberculosis
	22.5.30	45	—	—	25	—	—	1.2	-14	—	
	25.6.30	45	6.5	-10	24	172*	—	1.0	-29	Moderate	—
M. G.	29.9.29	21	10.5	—	21	+17	—	1.5	—	—	Rheumatic
	12.10.29	45	8.5	-20	24	+6	-11	1.6	+6	Moderate	
J. Sr.	23.7.29	21	12.3	—	24	+9	—	3.3	—	—	Rheumatic
	29.7.29	21	9.3	—	25	+2	—	3.3	—	—	
	6.8.29	21	11.4	—	24	+2	—	3.0	—	—	—
	13.8.29	45	11.6	—	24	+10	—	2.6	—	—	—
23.8.29	45	11.3	0	22	+7	+5	2.8	-15	None	—	—
A. S.	28.3.30	21	9.4	—	20	181*	—	2.0	—	—	Congenital
	1.4.30	45	10.5	+10	20	200*	+11	2.5	+25	None	

\* Figures give CO<sub>2</sub> output, c.c. per min.

# VI. *Analysis of Particular Phases of Response to High Oxygen*

In the whole series of twenty-eight cases, there were naturally great variations in response to oxygen therapy, depending on the type of cardiac or pulmonary disease present, and upon other factors. It will be convenient to consider now the available data from all our cases, covering in detail the responses to oxygen therapy in respiratory, circulatory, renal, and metabolic functions. In this way certain differences in reaction of particular types of heart disease can be brought out.

*Oxygen therapy: effects on respiratory function.* In seven of the cases of our series, comparative measurements of pulmonary ventilation (under basal conditions) were made. Table IV gives the relation of pulmonary ventilation in these subjects, to their metabolic rate and certain other functions. It will be noted that in the five patients in whom clinical improvement took place, pulmonary ventilation was decreased when the patient was in high oxygen. In those who were not improved, it did not occur. It is noteworthy also, from this Table, that the respiratory rate and other respiratory functions were less constant in their changes, during the period of oxygen treatment than was pulmonary ventilation. The development of light, rapid, shallow breathing early in the course of oxygen inhalation was noted by Beddard and Pembrey (20).

The relief of subjective dyspnoea was a constant phenomenon in all the cases of the series who improved. Though a change became apparent within an hour or so, the respiration was only gradually restored to normal, as was well shown by one patient. Ten of the twelve cases of arteriosclerotic heart disease, and all five cases of chronic pulmonary fibrosis, with secondary cardiac symptoms, were relieved of dyspnoea. The other two cases of arteriosclerotic heart failure did not suffer from this symptom. Four of the patients had Cheyne-Stokes respiration; this was restored to normal rhythm in every instance, though usually only after several days.

Of the ten cases of rheumatic heart disease with dyspnoea, two were markedly relieved within a few hours after transfer to the oxygen room; three others were partly relieved, the remaining five were not improved.

There was no constant change in vital capacity during the course of oxygen treatment. In a few instances there was an increase within the first few days. Three patients showed a decrease of 200 to 600 c.c., in spite of the fact that they were improving at the time.

In several cases (not recorded in the Table) there was a gradual increase in vital capacity, beginning in the second week of oxygen treatment and progressing for several weeks, coincident with steady general improvement. The tendency to lower basal metabolic rate, with improvement, has long been known (24).

*Oxygen therapy: effects on the blood.* (a) *Oxygen.* We did not determine, in any case of the present series, how quickly after the patient's transfer to the oxygen room, increase in arterial oxygen saturation took

place. Other investigators have found an increase to occur within an hour or less. The arterial blood samples were taken twenty-four hours or more after transfer to the oxygen room. At this time, in most cases measured, the arterial oxygen saturation had reached nearly its maximum level, as illustrated by L. S.

In the group of nine cases of arteriosclerotic heart disease on whom successive arterial oxygen measurements were made, the saturations under normal atmospheric conditions varied between 80 and 95 per cent. (Table V). In eight cases these saturations were raised, during oxygen therapy, to from 96 to 100 per cent.; these patients were all clinically improved. In one case, E. S., arterial saturation was changed only from 92 to 93 per cent. in oxygen. She was not improved.

In the pulmonary fibrosis group, of four cases so studied, three had arterial oxygen saturations returned to normal levels or above on the first blood examination in high oxygen. The fourth and most severe, J. Sn., was studied on numerous occasions. In normal atmosphere, his saturation was low, varying from 85 down to 65 per cent. depending on his degree of pulmonary insufficiency. He was always relieved by oxygen therapy; sometimes nasal catheter inhalations were sufficient, often the high concentrations in the tent or chamber were necessary. His saturation could in this way be brought up to from 90 to 95 per cent.

In the group of cases of rheumatic heart disease, the relation between increase in arterial oxygen saturation and improvement in clinical condition, did not follow the two groups just considered. This is shown in Table V. Two of the patients, for example, I. B., and C. D'Esp., were considerably improved when their arterial oxygen saturations were raised. Two others, F. T. and N. G., whose arterial saturations were also raised above normal, were only slightly more comfortable in high oxygen, but otherwise unchanged. On the other hand, F. M. had satisfactory increase of arterial oxygen saturation, and yet continued to fail rapidly, and died in a few days.

The high saturation of arterial oxygen in most of the patients while in the oxygen chamber, combined with the facts that their blood  $\text{CO}_2$  values were increased, and serum pH little changed, indicated high arterial oxygen tension, and thus readier transfer of oxygen from blood to tissues. Whether tissue oxygen tensions, during his oxygen breathing, were above normal or were still low, depended upon the rate of blood-flow. On this point we have no adequate data.

(b) *Blood carbon dioxide.* Rise in blood  $\text{CO}_2$  values was the most definite and consistent of the blood changes in all the cases who showed improvement through oxygen treatment. The increase was both a rise in arterial  $\text{CO}_2$  content and in the level of the dissociation curve. Of twenty-five patients on whom this measurement was made, before and during oxygen treatment, eighteen showed definite clinical improvement, and all of these had also a rise in arterial whole blood  $\text{CO}_2$  content, the amount of the

increase varying from 2.1 mol. equiv. up to 14.1 mol. equiv. The average increase was 5.4 mol. equiv. One of the seven patients who were not appreciably improved in high oxygen showed a small increase of 3.6 mol. equiv., in arterial  $\text{CO}_2$ . One showed a considerable decrease of 7.0 mol. equiv. The changes in the arterial whole blood  $\text{CO}_2$  content of the other five patients were insignificant.

As shown in Table V, in a number of instances the arterial blood  $\text{CO}_2$  was determined several times during the patient's course in the oxygen chamber or tent. The tendency seemed to be for the  $\text{CO}_2$  to increase for several days, to remain for a time at the high level, and then with continued improvement, to decrease again. In three cases, in whom vital capacities were also followed, a progressive rise in this function began at about the time when the  $\text{CO}_2$  level began to decrease.

In three instances it was possible to measure the arterial  $\text{CO}_2$  levels during progressive withdrawal of oxygen, from patients who were still in need of it. The blood  $\text{CO}_2$  decreased sharply, as the oxygen in the inspired air was lowered.

Reference to Table V shows the further interesting fact that the  $\text{CO}_2$  values sometimes rose to excessively high level. We have noted this fact in earlier publications (1); as also have Katz, *et al.* (7). In six instances the values of arterial whole blood  $\text{CO}_2$  content were over 30 mol. equiv.; five of these patients were cases of advanced pulmonary fibrosis, the sixth had a large hypertensive heart with congestive failure. The patient who demonstrated this phenomenon most dramatically was R.B., a woman of 48, with long standing and progressive pulmonary fibrosis. At the end of seven months in 40 to 60 per cent. oxygen atmosphere, when her tidal air was 200 c.c., and vital capacity 250 c.c., her arterial whole blood  $\text{CO}_2$  content reached the remarkable, if not unprecedented, level of 59.4 mol. equiv., or 132 volumes per cent.

It should be mentioned that the atmosphere in the oxygen chamber was not entirely free from  $\text{CO}_2$ , but contained usually about 0.5 per cent. of this gas, occasionally as high as 1.0 per cent. This was not, however a determining factor in the  $\text{CO}_2$  increase in the blood, as shown by the facts (a) that the same increase occurred when in certain instances oxygen was administered by nasal catheter, (b) that the blood  $\text{CO}_2$  decreased if the oxygen concentration in the chamber was decreased, and (c) that patients who remained in the chamber for several days at normal (21 per cent.) oxygen concentrations showed no increase in blood  $\text{CO}_2$  values.

(c) *Carbon dioxide tensions and serum pH.* In nine instances determinations were made of the  $\text{CO}_2$  dissociation curves of oxygenated arterial blood before and during oxygen treatment. From these and the arterial whole blood  $\text{CO}_2$  contents, serum pH values were calculated. In every case but one, the  $\text{CO}_2$  curves increased to about the same extent as the arterial  $\text{CO}_2$  contents, and the serum pH levels therefore remained nearly constant. In five of the cases who improved during oxygen treatment there was a small

TABLE V

*Variations in Arterial Blood O<sub>2</sub> and CO<sub>2</sub> Values, with Variation in O<sub>2</sub> of Respired Air.*

Patient. Case No.	Date.	Oxygen % in air.	Arterial whole blood.			
			O <sub>2</sub> content vol. %.	O <sub>2</sub> capacity vol. %.	Satura- tion %.	CO <sub>2</sub> content mol. equiv.
(a) <i>Arteriosclerotic heart disease.</i>						
1. A. L.	6.7.29	45	18.0	18.7	96	24.0
	16.7.29	25	17.8	19.5	91	20.2
2. L. S.	7.9.30	21	16.6	19.7	84	19.9
	8.9.30	25	15.0	17.5	86	20.2
	9.9.30	40	17.3	18.0	96	22.1
	10.9.30	40	17.9	18.1	99	22.6
	11.9.30	45	17.6	18.0	98	23.7
	13.9.30	44	17.1	17.5	98	24.5
	19.9.30	45	17.9	17.9	100	22.8
	21.9.30	45	—	—	—	22.3
	30.9.30	21	19.1	20.0	95	20.6
3. L. C.	24.6.33	21	17.6	18.6	96	20.7
	6.7.33	45	15.4	15.5	100	25.7
4. S. H.	7.4.33	21	16.2	20.2	80	25.5
	10.4.33	45	18.4	18.8	98	28.6
	17.4.33	21	16.1	19.4	83	28.1
	24.4.33	21	16.3	19.1	85	27.8
5. E. A.	22.4.31	21	16.3	17.5	93	29.5
	29.4.31	45	16.4	16.3	100	35.3
6. J. M. Q.	16.8.29	21	—	20.7	—	18.3
	30.8.29	45	—	17.6	—	26.1
	6.9.29	20	—	16.5	—	25.2
	25.9.29	35	—	—	—	24.1
	5.10.29	21	14.5	17.4	83	22.6
8. C. S.	19.1.33	21	19.7	21.4	92	21.7
	2.2.33	45	18.2	19.5	93	14.7
9. H. S.	24.6.32	21	13.1	14.5	90	22.6
	1.7.32	45	16.8	16.8	100	25.2
10. G. K.	25.10.32	21	19.5	20.6	95	17.5
	1.11.32	45	21.5	21.6	100	24.9
11. J. L.	26.9.30	21	20.6	22.0	94	20.9
	3.10.30	45	22.0	22.3	99	23.0
(b) <i>Rheumatic heart disease.</i>						
13. C. D'E.	29.10.31	25	18.2	19.9	91	17.7
	31.10.31	45	—	—	—	—
	2.11.31	21	18.6	19.7	94	24.1
	9.11.31	45	18.3	19.9	92	22.0
	12.11.31	45	18.3	18.5	99	24.6
	20.11.31	45	16.1	16.8	96	26.7
14. M. G.	20.9.29	21	16.9	—	—	—
		45	17.3	19.9	87	21.8
15. I. B.	27.9.29	21	19.3	23.0	84	16.7
	12.10.29	45	22.8	24.4	93	18.5
	15.10.29	25	19.7	23.5	84	11.8
	19.10.29	45	21.3	21.8	98	22.0
16. N. B.	7.11.30	21	16.1	17.7	91	22.2
	12.11.30	45	14.6	—	—	25.2

TABLE V (continued)

Patient. Case No.	Date.	Oxygen % in air.	Arterial whole blood.				
			O <sub>2</sub> content vol. %.	O <sub>2</sub> capacity vol. %.	Satura- tion %.	Co <sub>2</sub> content mol. equiv.	
(b) <i>Rheumatic heart disease (continued)</i>							
17. F. T.	19.10.32	21	13.1	14.2	92	19.9	
	2.11.32	45	14.9	14.9	100	23.4	
	23.11.32	21	14.2	15.0	95	20.9	
18. N. G.	11.10.32	21	17.4	18.9	92	23.2	
	17.10.32	21	17.6	18.5	95	23.5	
	11.11.32	45	16.3	16.6	98	26.3	
	24.11.32	21	15.7	17.9	88	23.8	
19. F. M.	7.11.30	21	19.8	21.9	90	19.4	
	12.11.30	45	20.5	21.4	96	18.5	
20. J. Sr.	23.7.30	21	18.3	20.4	90	19.7	
	29.7.30	21	20.9	21.6	97	20.7	
	6.8.30	21	20.0	21.0	95	19.4	
	13.8.30	45	20.8	—	—	20.8	
(c) <i>Pulmonary fibrosis.</i>							
22. J. Sn.	23.12.29	21	17.1	24.2	71	15.9	
	28.12.29	21	16.6	23.9	69	17.2	
	2.1.29	45	16.2	—	—	31.4	
	6.1.29	45	16.5	18.4	90	30.2	
	19.1.29	25	17.8	19.0	94	25.5	
	25.1.29	25	16.0	18.4	87	23.6	
	6.3.29	25	16.9	19.7	86	21.9	
	27.3.29	21	11.7	18.0	65	—	
	9.11.31	21	20.0	23.7	84	22.2	
	12.11.31	45	21.2	22.6	94	26.2	
	20.11.31	45	—	—	—	32.6	
	24.11.31	45	22.4	24.4	92	26.4	
	7.1.32	25	17.3	21.2	82	23.6	
	23. J. W.	20.5.32	21	18.4	20.5	90	25.6
		31.5.32	45	19.5	20.0	98	32.0
3.6.32		45	—	—	—	29.9	
24. I. S.	2.5.30	21	17.8	20.3	88	24.6	
	22.5.30	45	18.2	19.4	94	32.3	
	25.6.30	45	16.7	18.0	93	33.0	
25. P. W.	25.6.32	21	16.0	18.0	89	25.3	
	7.7.32	45	17.2	17.0	100	28.1	
	15.7.32	45	14.6	15.9	92	31.0	
	19.7.32	45	16.2	16.3	100	31.2	
	29.7.32	45	15.3	14.7	100	34.7	
	12.8.32	45	14.5	14.9	97	29.3	
	30.8.32	25	12.8	14.0	91	28.8	
26. R. B.	2.9.30	50	12.3	14.1	87	59.2	
	3.9.30	50	7.2	14.4	50	53.8	
(d) <i>Congenital heart disease.</i>							
27. A. S.	13.3.31	21	20.3	31.7	64	—	
	18.3.31	21	18.5	33.8	55	34.2	
	28.3.31	21	20.2	33.8	60	38.6	
	1.4.31	45	21.5	33.2	65	40.0	
28. J. Sch.	25.3.31	21	17.4	18.4	95	21.8	
	29.3.31	45	18.2	18.5	98	23.1	

shift, of about 0.02, to the alkaline side. In only one was the increase in pH's of significant extent. This patient, I. B., was a woman with rheumatic heart disease, in a stage of extreme congestive failure, who had been treated in the oxygen room, but was then removed from the chamber too abruptly. She sank rapidly into a condition of shock in the next ten hours, her blood  $\text{CO}_2$  sank to 11.8 mol. equiv. and arterial pH to 7.36. On her return to the oxygen chamber, her arterial  $\text{CO}_2$  rose again to 22.0 mol. equiv., and arterial pH's to 7.46.

Similar measurements were made on patient J. Sn. during progressive withdrawal of oxygen inhalations (see below). Again the pH changes were small. During the first two weeks of this progressive withdrawal, when the arterial  $\text{CO}_2$  content decreased from 28.9 mol. equiv. to 25.8 mol. equiv. the pH remained practically constant, between 7.41 and 7.44.

In general, the arterial pH values in this series are remarkable for their constancy, in view of the marked changes in  $\text{CO}_2$  levels that took place, as well as the changes in clinical conditions.

(d) *Serum electrolytes.* The state of the electrolytes and water of the blood-serum at any time is obviously a resultant of many forces: of the respiratory gases, of tissue electrolyte and water concentrations, of circulatory pressures, volumes, and flow, of renal and other excretory activity, and so forth. In the progressive and relatively gradual adjustment that takes place when a cardiac patient improves in high oxygen, there are presumably extensive and complex changes in most of these forces. A knowledge of the progressive changes in the serum may give some indication as to predominant factors in certain phases of the process, particularly during the peculiar latent period that often occurs between restoration of arterial oxygen saturation, and onset of diuresis. Our data on serum electrolyte values are unfortunately fragmentary. We wish to review at this point the serum studies made on patient L. S. with particular reference to coincident phenomena, such as (a) oxygen concentration in the inspired air and resulting blood-gas values, (b) urinary output of water and electrolytes, (c) venous pressures. The combined data have been presented in Table III.

The following facts are apparent, from the Table:

1. During the first three days of oxygen therapy, there was a fall in serum total base, and slight fall in protein of the serum, these two changes being approximately proportional when considered as percentage changes in concentration. Serum protein concentrations were followed in two other instances in this series. In both there was a similar decrease following the institution of oxygen therapy.

2. There was in the same interval a somewhat more marked drop in serum chloride; a rise in  $\text{CO}_2$  (already described); a slight fall in lactic acid.

3. Change in oxygen capacity of the blood was indeterminate, on account of wide variation in control period values. Five other cases (see Table V) had oxygen capacity measurements made during the first few days in high

oxygen, before diuresis was established; all of these showed significantly lower values than in the control period.

It is to be noted that the above changes all occurred while there was only a slight increase in urinary water output, and consistently low urinary chloride output.

4. During these first three days venous pressure was at a level about 50 to 60 mm. lower than in the control period.

5. With the sudden increase in chloride output, and later in water output, that began on 12th September, there was no demonstrable further change in serum electrolytes, in venous pressure, or in oxygen capacity.

6. After diuresis was over and oedema had disappeared, serum protein and oxygen capacity were found to be increased again; total base still low; chloride slightly increased;  $\text{CO}_2$  decreased again.

It is not possible to give an explanation for all these changes. The simplest way to account for the initial drop in base, protein, and oxygen capacity is to suppose that there occurred a dilution of serum with water. The serum electrolyte changes, though small, are greater than could be accounted for by the slight shift in electrolytes and water between red-blood cells and serum, due to increased oxygenation of haemoglobin. Chloride suffered a still further decrease; the excess of chloride thus lost from the blood would amount to approximately 1 grm., and so should have been detected, had it been excreted in the urine. The amount, however, is small, and whether it was excreted in another manner, or transferred to the tissues, can only be conjectured.

Lactic acid evidently played a minor part in the serum adjustments of the patient L. S. In another case (J. Sn.) the control period lactic acid was 22.7 mg. per 100 c.c., or 2.5 mol. equiv. It decreased to 7 mg. per 100 c.c. or 0.8 mol. equiv., during the first week in the oxygen chamber. Even these values are not great, and indicate that this substance is probably not an important factor in the serum electrolyte changes that take place during oxygen therapy.

*Oxygen therapy: effects on urinary water and chloride output and clinical oedema.* Nineteen of the patients in the series had, upon transfer to the oxygen room (or tent), large amounts of peripheral oedema; several had also ascites or hydrothorax. Nine of the nineteen were suffering from arteriosclerotic heart disease, eight had chronic rheumatic heart disease, one had cardiac insufficiency secondary to pulmonary fibrosis, and one had coarctation of the aorta, with terminal congestive failure.

Seven of the nine patients with arteriosclerotic heart disease and oedema had a diuresis with a complete loss of all oedema, in the course of oxygen treatment; one had a partial diuresis; while the ninth was unaffected. The patient with pulmonary fibrosis was on two occasions rendered free of oedema during the course of several weeks of oxygen therapy. Of the eight cases of rheumatic heart disease only one had a partial diuresis during oxygen treatment, the remaining seven were clinically unchanged in respect

to their oedema. The case of coarctation of the aorta had a diuresis on his fourth, fifth, and sixth days in the oxygen chamber, but died two days later.

In three of the cases who had a diuresis, urinary chloride output was measured daily. As would be expected, there was a large increase during the course of the diuresis. In one case (L. S.) there was a sharp increase in chloride output three days before a corresponding rise in urinary water excretion, in the other two cases water and chloride output increased at about the same time.

Of the twelve instances in which diuresis took place, the increased urinary excretion began on the first day in the oxygen room in two patients, on the second day in four, on the fourth day in one, on the sixth day in four, and on the seventh day in one. It is, of course, difficult to determine the exact time of onset of a gradual increase of urinary output, in view of normal daily variations. The day when the 'increase' began has been taken arbitrarily as the first day in which urinary output exceeded total fluid intake; in several instances there was probably an increase a day or two before this.

*Oxygen therapy: effects on venous pressure, arterial pressure, and pulse-rate.* The venous pressure levels during the course of oxygen treatment were followed in five patients, as shown in Table VI. All the patients had oedema; the first two cases listed in the Table were greatly improved and lost all oedema in 45 per cent. oxygen, the third had a moderate diuresis, the other two were not appreciably improved. The figures show the following:—(a) diuresis did not occur when the venous pressure was over 200 mm.; (b) diuresis began, in three instances, while the venous pressure was still elevated, and was between 130 mm. and 180 mm.; (c) the case who showed the most abrupt and massive outpouring of water had a sharp drop of venous pressure to normal levels, coincident with the onset of this large diuresis. Single observations (not included in the Table) on other patients showed venous pressures within normal limits following diuresis and recovery of compensation.

The pulse-rate usually dropped gradually during the first few days in high oxygen, in patients with sinus rhythm.

There appeared to be no consistent alteration in systolic or diastolic arterial blood-pressure as a result of the high oxygen atmosphere.

It may be noted that our observations in the general field of circulatory dynamics were by no means comprehensive; we made no studies of blood-volume, volume-flow, or velocity of blood-flow; nor any comparative study of electrocardiographic changes.

*Effects following return of patients from high oxygen to normal atmospheric air.* The usual procedure employed when a patient was to be removed from 40 per cent. oxygen to room air, was to reduce the air in the chamber to 35 per cent. for a day, then to 30 per cent. for a day, then to return the patient to the ward, oxygen being given by nasal catheter for several days thereafter.

On this régime, of ten cases in the group who were restored to ambulatory activity, three suffered mild symptoms of anoxaemia for one or two days following return to atmospheric air; two others, who had pulmonary fibrosis, required a long period of further treatment with oxygen by nasal catheter. The remaining five accomplished the transition from 40 per cent. to 21 per cent. oxygen without symptoms.

Of the ten cases who were improved but failed to recover compensation in high oxygen, all but one suffered, during the days following return to room air, some increase in symptoms,—dyspnoea, cyanosis, orthopnoea, oedema. In six instances this process was a gradual relapse, extending over a number of days, to the patient's condition before oxygen treatment was started. One patient suffered sudden collapse, with acute anoxaemia, because of removal from the oxygen room without an acclimatization period. Two patients were extremely dyspnoeic whenever the respired oxygen concentration was decreased; both eventually died in the oxygen chamber.

In the eight cases who were not improved in high oxygen, transfer back to room air made no appreciable difference in symptoms.

A few cases developed a mild anaemia during oxygen therapy, the anaemia persisting for some weeks thereafter. This was not sufficient to cause symptoms.

In general it may be said that after a return to room air, following the period in high oxygen, all patients were either better than they had been before oxygen treatment began, or else their condition was unchanged. We found no evidence that the period in high oxygen had destroyed a beneficial 'adaptation' to chronic anoxaemia (3).

## VII. Discussion

The above data, considered as a general description of the physiological response of an individual with cardiac or pulmonary failure to increased oxygen concentration in the respired air, are obviously incomplete. The most important measurement that is lacking is probably the cardiac output. As is well known, no method that is both reliable and free from risk to the patient, is at present available for measurement of this function in cases with marked pulmonary insufficiency.

It seems justifiable, nevertheless, on the basis of the facts obtained, for us to attempt a tentative description of the mechanism whereby, in favourable cases, a failing cardio-respiratory apparatus may be restored to compensation under the influence of increased respired oxygen concentration. For this purpose we shall consider specifically the state of congestive failure with oedema, such as occurs in elderly patients with arteriosclerotic heart disease.

The physiological disturbances that exists in this condition have been extensively investigated in recent years. We may state as follows the present concept of the state of congestive heart failure:—

Weakness of left ventricular muscle leads to dilatation of the ventricle (21), increased mean left auricular pressure, diminished ventricular output (22),

TABLE VI

*Venous Pressures, Relation to Atmospheric Oxygen, and Bodily Water Balance*

Patient.	Date.	O <sub>2</sub> in atmo- sphere %.	Venous pressure mm. H <sub>2</sub> O.	Intake minus out- put c.c. per day.	Body- weight kg.	Clinical Oedema.
L. S.	8.9.30	25	190	+ 645	—	Marked on legs and body
	9.9.30	45	140	+ 550	—	Same
	10.9.30	45	130	+ 800	—	Same
	12.9.30	45	150	+ 250	—	Same
	13.9.30	45	140	+ 400	—	Same
	17.9.30	45	130	- 330	—	Definite decrease
J. Sn.	8.11.31	21	136	+ 725	—	Marked on legs and sacrum
	9.11.31	21	191	+ 550	67.8	Same
	10.11.31	21	172	+ 850	—	Same
	11.11.31	45	195	+ 240	—	Same
	12.11.31	45	180	+ 440	—	Same
	13.11.31	45	135	+ 500	69.0	Same
	14.11.31	45	170	+ 400	69.0	Same
	16.11.31	45	180	- 460	68.1	Salt poor diet, 11.16 p.m.
	18.11.31	45	135	- 1050	65.9	Same
	19.11.31	45	52	- 2615	—	Less
	20.11.31	45	62	- 2750	60.0	Less
	29.11.31	25	65	+ 25	53.6	Oedema gone on 11.23
C. D'Esp.	29.10.31	25	240	+ 525	—	Massive, with ascites
	31.10.31	45	—	- 370	—	Same
	10.11.31	25	168	+ 660	—	Same
	11.11.31	45	175	+ 550	—	Same
	12.11.31	45	120	+ 760	—	Same
	13.11.31	45	145	- 50	61.8	Same
	15.11.31	45	168	+ 20	61.3	Same
	17.11.31	45	162	- 620	60.9	Same
	19.11.31	45	165	- 520	60.0	Less, ascites less
	20.11.31	45	137	- 550	59.0	Less
	23.11.31	45	—	+ 60	58.7	Less, but much remains
	27.11.31	25	—	- 435	59.0	Same
N. G.	4.11.32	45	210	+ 475	—	Ascites, leg oedema
	12.11.32	45	250	+ 1025	—	Developing hydrothorax
	18.11.32	21	190	+ 955	42.3	Leg oedema less
	25.11.32	21	220	+ 275	42.3	Same
F. T.	4.11.32	45	150	+ 580	—	Increasing as- cites, no leg oedema
	12.11.32	45	173	+ 1250	—	Same
	18.11.32	21	200	+ 850	60.0	Same
	25.11.32	21	215	+ 750	59.5	Same
	22.12.32	21	243	+ 685	57.7	Same
	13.1.33	21	200	+ 660	61.8	Same

and diminished velocity of blood-flow (23). In the lungs, due probably in great part to congestion and overfilling of the pulmonary blood depot, there is stiffening of pulmonary tissues, with increased respiratory effort, increased resting ventilation—often laboured and abnormal in character—decreased vital capacity (24), and total ventilation capacity (9), imperfect mixture of pulmonary gases (25), imperfect aeration of pulmonary blood. The arterial blood thus frequently shows increased oxygen unsaturation (1, 7). Blood  $\text{CO}_2$  and pH changes are variable (1, 7). Decreased cardiac output diminishes still further the venous (and tissue) oxygen content, and leads to increased tissue and blood lactic acid (26). The chemical stimulus in the respiratory centre is increased. Pulmonary congestion and weakness of right ventricular muscle leads to increased right auricular pressure, increased peripheral venous pressure (15), increased total blood volume (27), tissue congestion and oedema. Renal and nutritional abnormalities may contribute to the oedema formation (28).

Increased oxygen concentration in the inspired air will obviously lead first to increased oxygen tensions in the ventilated parts of the lungs, and to some extent, by diffusion, in unventilated parts. Arterial oxygen saturation will then increase. Tissue oxygenation will on this account be improved; there will be less lactic acid formation. Decreased fixed acid releases base, and bicarbonate increases. The respiratory stimulus is presumably decreased. Pulmonary ventilation is less; the actual form of respiration is light and shallow, with little change in rate. This, in turn, provides less adequate  $\text{CO}_2$  elimination, and the alveolar and arterial  $\text{CO}_2$  tensions increase. The resultant effect on arterial pH is small.

How much the cardiac output improves, following the initial increase in arterial oxygen saturation, is not known. The slowing of the pulse-rate, and the clinical fact that the pain of angina pectoris may be relieved following oxygen inhalation, suggest, at least, that such improvement may be an early effect. If so, tissue oxygenation will be still further improved.

Other changes in blood and vascular system occur within the first twenty-four hours. Venous pressure either decreases or remains constant. There is apparently a dilution of the blood; our data on this point are not numerous, but are all consistent with this interpretation, except for one or two blood measurements in the oxygen-withdrawal experiment. Fall in venous pressure and haemo-dilution indicate widening of the blood bed—perhaps a further dilatation of blood depots. The decrease sometimes observed in vital capacity at this time suggests that the pulmonary blood depot may also be further widened.

During the first few days there is a progressive increase in blood  $\text{CO}_2$ , much in excess of that needed for lactic acid replacement. The fact that this same phenomenon occurs to an even more marked extent in cases of chronic pulmonary disease, without congestive failure, suggests that pulmonary dysfunction—shallow, inefficient respiration, relative increase in residual air—is the primary factor in this  $\text{CO}_2$  change. With the rise in

CO<sub>2</sub> occurs a corresponding decrease in blood Cl; the chemical explanation of this adaptation is not clear. Serum pH remains little changed. The resultant high level of arterial and alveolar CO<sub>2</sub> tension is advantageous for pulmonary function, as it provides high CO<sub>2</sub> elimination per unit volume of ventilation.

At a variable time in the first week of oxygen therapy, from the second to the seventh day, urinary output of water and chloride begins to increase, rises to a maximum in the following week, then gradually regresses, as excess body fluid is disposed of. Several factors probably enter into the production of this diuresis. Passage of fluid from capillaries to tissues should be decreased on account of higher oxygen tension and lower venous pressure (30). Improved oxygenation should improve renal tissue function. How much the gradually progressive character of the diuresis is associated with gradual increase in cardiac output can only be conjectured. It is possible that release of chloride may have a diuretic effect, in a manner analogous to the action of ammonium chloride or potassium chloride.

As the diuresis proceeds and oedema is disposed of, there appears to be a gradual concentration of serum, as evidenced particularly by increase in serum protein and in oxygen capacity; this is presumably a part of a general loss of bodily water excess. Total base, on the other hand, does not increase appreciably, probably due to general loss of base with water. Chloride increases somewhat, and HCO<sub>3</sub> decreases.

It is of interest to compare the description above given, of compensation restored by the aid of oxygen, with the phenomena that occur when a case of congested heart failure recovers compensation without oxygen treatment. The pattern of response is similar. Pulmonary ventilation decreases. Arterial oxygen saturation increases. Blood CO<sub>2</sub> levels increase. Venous pressure falls. At a variable time after improvement begins, diuresis sets in.

The chief difference is the greater quantitative increase in arterial oxygen saturation, increase in blood CO<sub>2</sub>, and decrease in blood Cl, that takes place in the oxygen-treated cases. Whether these alterations exert any specific influence upon the bodily electrolyte and water balance, cannot be stated.

The blood dilution that apparently occurred early in the course of treatment in certain of our cases, has been a frequent but not consistent finding in previous studies of patients with congestive failure not treated with oxygen (28).

For the present, we must be content with the statement that oxygen therapy acts in cardiac insufficiency chiefly by supplying to the tissues one greatly needed element: that it breaks at one point the vicious circle of congestive failure and enables vital processes to be carried on, with a minimum of circulo-respiratory effort, until the restorative processes of the body become effective.

The comparison just made emphasizes the importance of oxygen want as a factor in chronic cardiac as well as chronic pulmonary insufficiency.

### VIII. *Clinical Results*

A. *Arteriosclerotic heart disease.* Eight patients with congestive failure and oedema were treated in oxygen after other measures had failed. Four recovered compensation, and became ambulatory. Three were improved but later failed and died without recovering compensation. One was not improved and died in four days.

Two patients with congestive failure and oedema were treated on admission both with oxygen and with other measures. Both recovered compensation.

One patient with coronary thrombosis and one with almost continuous attacks of angina pectoris were given oxygen therapy. Both improved, and recovered compensation.

B. *Rheumatic heart disease.* Eight cases with congestive failure and oedema, and one case of chronic mitral disease with liver enlargement but without oedema, were treated in oxygen. Several were relieved of dyspnoea, one had a partial diuresis, none was restored to ambulatory activity.

C. *Pulmonary fibrosis with cardio-respiratory insufficiency.* All five cases in this group were relieved of dyspnoea and rendered free of symptoms after being placed in 50 per cent. oxygen. Two of the patients who were restored to ambulatory activity later had a return of symptoms, and were again restored to limited compensation following prolonged oxygen treatment. Two patients were improved and able to leave the oxygen room, but did not recover compensation. The fifth patient died in the oxygen room after seven months' continuous residence.

In brief, from this series one may conclude that prolonged, continuous oxygen therapy will frequently restore to limited compensation a patient with arteriosclerotic heart disease and insufficiency (not complicated by chronic nephritis), that it may increase the comfort and relieve dyspnoea in a case of decompensated rheumatic heart failure, that it will usually relieve symptoms in chronic pulmonary fibrosis with cardio-respiratory failure, and may, if sufficiently prolonged, restore such a case to limited ambulatory activity.

*Indications for oxygen therapy.* On theoretical grounds, the tissue 'oxygen deficit', as determined by Uhlenbruck and other German investigators, is probably the best criterion of the need for increased oxygen in the respired air. The work reported in the present paper was completed before we were aware of the clinical importance of this measurement.

Arterial oxygen saturation is not a certain index of oxygen want. It is true that if the arterial oxygen saturation is depressed below normal, then oxygen therapy is definitely indicated. But symptoms of oxygen want often exist even when arterial oxygen saturation is within normal limits, and these may be relieved when the patient is placed in an atmosphere of 50 per cent. oxygen. Arterial oxygen saturation in such cases usually rises to 97 per cent. or above.

Clinical cyanosis is a poor criterion of the degree of oxygen want. Marked

arterial oxygen unsaturation may exist when clinically cyanosis appears slight. Conversely, deep cutaneous cyanosis may be present with normal arterial oxygen saturation, and without general symptoms of oxygen want. In such cases response to oxygen therapy may be poor.

The best practical estimate of the need for oxygen treatment can be made from clinical observation. The following symptoms and signs, in relative order of importance, will establish the need for increased oxygen in the respired air, for patients with chronic cardiac or pulmonary insufficiency.

1. *Dyspnoea.* This includes continuous dyspnoea, orthopnoea, paroxysmal or nocturnal dyspnoea, Cheyne-Stokes respiration.

2. *Restlessness.* This includes apprehension, insomnia, and various disturbed mental states. Patients often sleep most of the time during the first few days in high oxygen.

3. *Cardiac pain,* particularly of the anginal type. Some relief of cardiac pain is usually obtained after the second or third day in high oxygen; but coronary attacks may not be completely prevented.

4. *Arterial oxygen unsaturation.*

5. *Cyanosis.*

6. *Cough,* whether in cases of congestive failure, or of chronic pulmonary disease.

One practical consideration in the oxygen treatment of this group of diseases requires final emphasis. Oxygen must be given, not only for long periods, but in high concentration. In our experience, with patients severely decompensated, oxygen by nasal catheter is usually insufficient; the 40 to 50 per cent. concentration, provided by the tent or the oxygen chamber, is necessary.

### *Summary*

1. Two normal men and twenty-eight patients in the cardiac insufficiency state have been kept in atmospheres of 40 to 50 per cent. oxygen for continuous periods ranging in length from five days to seven months. Studies have been made, in these subjects, of the effects of high oxygen atmospheres upon circulatory and pulmonary functions, and in certain instances upon their water and electrolyte balances.

2. Two normal subjects, residing for a week in 45 per cent. oxygen, showed a fall in pulse-rate, slight rise in blood  $\text{CO}_2$  levels; no appreciable change in respiratory metabolism, in cardiac output, or in excretion of electrolytes or water.

3. The response to high oxygen atmospheres, in favourable cases of congestive heart failure, was found to follow a fairly definite pattern or sequence of events. This has been described in detail.

- (a) *Dyspnoea* and *restlessness* were partly relieved within a few hours, but completely relieved only after several days.

- (b) *Arterial oxygen saturation* was restored to normal, or raised slightly

above normal, within the first twenty-four hours. Rise in blood  $\text{CO}_2$  began on the first day, then continued progressively for several days.

(c) Increase in urinary chloride and water excretion frequently occurred, beginning from one to six days after the beginning of oxygen treatment, then proceeding to complete loss of oedema.

4. The favourable response to prolonged oxygen treatment was found to be similar in general course to the recovery of compensation by other means, though definite differences in certain details were encountered. These have been further discussed.

5. Of twelve cases of arteriosclerotic heart disease, severely decompensated, eight were restored to limited ambulatory activity, following prolonged oxygen treatment, three were temporarily improved, one was not improved. Eight out of nine cases with oedema had a diuresis during their course in high oxygen.

6. Of nine cases of rheumatic heart disease severely decompensated, none was restored to ambulatory activity. Five cases showed moderate improvement and relief of symptoms, the remaining four were not appreciably improved.

7. Of five cases of pulmonary fibrosis with secondary circulatory insufficiency, all were improved. Two were restored to ambulatory activity.

8. The clinical indications for oxygen therapy, in relative order to importance, are: (a) Dyspnoea. (b) Restlessness. (c) Cardiac pain of anginal type. (d) Arterial oxygen unsaturation. (e) Cyanosis. (f) Cough.

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LUNG ABSCESS<sup>1</sup>

WITH SPECIAL REFERENCE TO CAUSATION AND TREATMENT

BY JAMES MAXWELL

*Introduction*

THE abundant, and in some respects conflicting, literature which has appeared in recent years upon the subject of pulmonary suppuration is eloquent testimony to the fact that, in this field at least, there are many points which have still to be elucidated, with reference both to aetiology and to treatment. The great majority of the recent papers on this subject have emanated from the United States, although it is by no means certain that the incidence of the condition is greater there than in this country.

The purpose of the present paper is to place upon record the results of a study of the post-mortem findings in a series of 315 cases in which suppuration had occurred within the lung, and to consider the bearing of these findings upon the problems of aetiology and treatment as they appear in the current literature. The material is derived from post-mortem records of St. Bartholomew's Hospital from 1907 to 1931, together with those of the Royal Chest Hospital, London, from 1922 to 1931. Every case in which suppuration was present within the lung tissue has been included in this series, with the exception of those cases in which tuberculosis appeared to be the sole cause; in this respect this series differs from the majority of those previously published, in that there has been no selection and that no cases are included which responded to treatment. In most papers the cases are selected on a clinical basis, and only cases in which the diagnosis was made during life are recorded; moreover, it is frequently stated that cases which have resulted from intrathoracic malignant disease have been intentionally omitted, a procedure which is, of course, justifiable in a clinical study, particularly if the results of treatment are to be considered.

It must therefore be borne in mind, when comparing the relative frequency of the various associated causal conditions recorded here with those previously reported, that certain invariably fatal cases will of necessity occupy a more prominent position in this than in other series not similarly constituted. With this exception, the aetiological factors should be reasonably comparable, for the results of treatment recorded by most observers leave much to be desired, and the mortality of all lines of treatment is still so high in every type of lung abscess that the aetiological causes remain in

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much the same proportion whether the cases be selected upon a clinical or upon a post-mortem basis.

For permission to make use of the notes of the cases in this series, I am indebted to Professor Kettle, of St. Bartholomew's Hospital, and to the members of the Staff of the Royal Chest Hospital.

### *Historical Review*

In order fully to appreciate the advances which have been made within recent years, and also to indicate the lines upon which this progress has been achieved, the following summary has been compiled from the literature and particularly from the historical reviews of Koch (189), Murphy (259), Aufrecht (9), Gluck (114), Hedblom (139), and Lockwood (218).

The condition was apparently well known to Hippocrates (149), who not only advocated the aspiratory theory by expressing the view that lung abscess is the result of inhalation of blood and mucus, but also advised thoracotomy for those cases in which the abscess has ruptured into the pleural cavity, giving rise to an empyema. He also recognized the possibility of cure by spontaneous rupture into a bronchus.

In 1584 Schenk (301) reported the promotion of spontaneous external rupture in a case of lung abscess by the application of fomentations. In the succeeding centuries the references became increasingly numerous. In 1664 Willis (367), in 1692 Purmann (283), and in 1696 Baglivi (12) advised drainage through an intercostal incision, and in 1726 Barry (18) reported recovery in two out of three cases treated by this method. Successful results following operation were also reported by Campardon (47) in 1759, and ten years later Sharpe (310) pointed out that the presence of adhesions is not a hindrance to treatment; and devised a method for the puncture of the abscess cavity through a small aperture. In 1783 David (73) and Pouteau (281) published observations, the latter insisting that a radical operation with full exploration of the abscess cavity was desirable; in 1793 Gumprecht (131), in discussing surgical procedures, pointed out that firm pleural adhesions should be present if drainage operations were to be successful, and in 1797 Faye (90) reported a cure following operation. It is interesting, however, to note that, according to Lockwood, the influence of Trousseau (333) was exerted in favour of palliative measures and against the more radical surgical procedures which were commonly employed at that time, on account of the unfavourable results of surgery as practised by his contemporaries.

In the early years of the nineteenth century Herff (144), Krimer (197), Hawthorn (138), and Stokes (321) successfully evacuated the contents of abscess cavities by means of a trocar and cannula, and Bell (22) in 1805, reported several failures and one cure by this method; successful results were also recorded by Richeraud (290) in 1812 and by Jaymes (173) in the following year. Callisen (45), in 1815, advocated a radical operation with

careful digital exploration in order accurately to define the limits of the cavity and to establish free drainage. Zang (379), in 1818, recorded eight operations, and further cases were reported by Breschet (37) in 1831, McLeod (232) in 1836, Claessens (56) in 1837, and Hastings and Störk (137) in 1844. Nasse (263) successfully operated upon several patients between 1824 and 1844, some of whom, probably, were cases of lung abscess. A case reported by Collins (65) in 1855 may have been an empyema or a lung abscess.

In 1853 Traube (332) published a study of the aetiological aspects of the subject, and in the same year Hildreth (148) described a case in which pulmonary gangrene followed the inhalation of a foreign body and was complicated by a spontaneous pneumothorax.

Green (121), in 1860, was the first to attack the condition by way of the air passages; he introduced catheters into the bronchi and injected chemical substances directly at the site of the lesion, but without satisfactory results. Maragliano (237), however, reported the cure of a chronic lung abscess of thirty years' duration following the intratracheal injection of a solution of silver nitrate; in 1864 a review was published by Koenig (190). In 1872 Waring-Curran (352) recorded a case of spontaneous cure after the abscess had ruptured through the diaphragm and tracked along the round ligament, discharging subsequently through the skin in the region of the umbilicus. Meantime, in 1867, Leyden and Jaffe (211) had published their observations on the bacteriology of pulmonary diseases, and it is of interest to note that they were the first to report the presence of spirilla in the foul sputum obtained from cases of bronchiectasis and lung abscess.

During the final decades of the nineteenth century attention was chiefly centred upon the development of thoracic surgery, and it is to the pioneer work performed during this period that we owe the comparative safety of present day intrathoracic surgical procedures.

In 1870 Jaszenko (172) studied the effects of penetrating wounds of the lungs, and during the next ten years Gluck (113), Schmidt (304), Block (33), and Biondi (31) showed that partial resection of the lung could be successfully accomplished in animals. Sutton (324), in 1881, reported a cure in a case treated by external operation, and in the same year Fenger (92) reported a cure in a case of his own, although he quotes other unsuccessful cases. In the following years Bull (40) published a series of papers on thoracic surgery, including a detailed study of fourteen cases of lung abscess, and about the same time Mosler (254) was the first intentionally to open a bronchiectatic cavity and to irrigate the diseased area. Cases were also reported by Finny (94) in 1884, and by Schmidt (304) and Block (33) in 1885, in which year, also, Truc (334) published a classical work. Two years later Runeberg (295) reviewed a series of eleven cases collected from the literature, of which two had recovered following operation; in 1893 Huber (159) recorded a successful operation for lung abscess in a child aged thirteen and a half months. Martius (239), in 1891, published a pathological study based on twenty-two cases examined *post mortem*. During the next few years further series of cases

were published by Garré (108), Quinke (284), Karewski (176) and Tuffier (336). The latter, in reviewing surgical treatment of lung abscess, reported forty-nine further cases in which operation had been performed. In 1901 Borchert (34) pointed out that, to ensure a successful operation, the exact limits of the lesion should be determined beforehand, and that no other foci of suppuration should exist in either lung.

In view of the subsequent developments in thoracic surgery, it is interesting to note that perhaps the earliest operation for removal of a major portion of the lung was carried out in this country by Lowson (225) in 1893; the operation was performed for pulmonary tuberculosis, and the patient is stated to have recovered.

It would seem, in view of the number of cases quoted, that lung abscess must have been a common condition during the last century, yet it is difficult to form any idea of its incidence, for many of the cases were included in more than one series, and in many others the diagnosis was open to question, thus causing the condition to appear more common than was actually the case. It is, however, difficult to credit the statement of Garré (108), that in the hundred years to 1893 only twenty-two authentic cases of lung abscess had been reported in the literature.

Finally, special mention must be made of the classical series of papers published by Murphy (259), in 1898, in which the position of thoracic surgery at the close of the nineteenth century is analysed and its limitations and defects clearly exposed. The discussion in these papers is very exhaustive, and the review of the contemporary literature is so complete that it is impossible to attempt a summary of Murphy's conclusions, but reference to the original papers shows that the basic principles on which the thoracic surgery of the present day is founded were already clearly established in his mind.

### *Definitions*

A part, at least, of the confusion which exists in the literature results from the fact that many writers employ the terms 'abscess' and 'gangrene' loosely, some regarding them as synonymous while others attach a different significance to each term. Some writers commence by defining their terms, but unfortunately in many instances the definitions bear no relation to those of other authors so that the confusion is little abated. Moreover, simplicity is an essential feature of any useful definition and, for the purposes of this paper, it will be sufficient to define abscess as 'non-tuberculous suppuration, with cavitation, occurring in the lung-tissue'.

The term 'gangrene' is much more difficult to define. In other parts of the body it usually suggests the presence of gross interference with the blood supply of the affected area, and in this sense the term can only be applied to comparatively few of the acute pulmonary lesions often described under this heading. In the sense in which it is usually employed the term 'pul-

monary gangrene' signifies cavitation and suppuration with characteristic foul pus; the condition is therefore included in the definition given here for lung abscess, and there does not appear to be any object in separating these cases into a special group. There is, it is true, a rare condition in which a complete lobe or more is affected as a result of embolism or thrombosis of a large branch of the pulmonary artery, and to which the term 'gangrene' might be justly applied. Yet in this type of case the term 'massive necrosis' would be even more appropriate, and by its adoption the use of the word 'gangrene' can be entirely avoided.

In addition, the term 'pulmonary suppuration' is becoming more commonly used. Inasmuch as there may be a suppurative condition of the lung present before the occurrence of cavitation constitutes the condition a true lung abscess, and also because the condition may apparently, in some cases, never progress to this stage on account either of the recovery or the early death of the patient, the term seems to be appropriate. It appears to have been employed first in 1911 by Guinon (128), who suggested the use of the phrase 'hepatisation grise suppurée' in a case which had occurred as a complication of pneumonia.

It will be necessary in later sections to discuss the various, and often conflicting, views of many writers. It is therefore desirable to consider at this stage the definitions which have been previously put forward.

Godlee (115) terms all abscesses of the lungs not due to tuberculosis or bronchiectasis 'gangrenous abscess'. Hedblom (139) considers that gangrene and abscess are not distinct clinically, but that there is a pathological distinction; Hamman (132) also classes the two conditions under one heading because there is no sharp distinction between them. Young (377) considers that gangrene occurs under the same conditions as simple abscess, but that it results either when the infection is especially virulent or the patient unduly debilitated, and Lockwood (219) includes moderate and localized gangrene under the heading of abscess. Powell and Hartley (282) stress the vascular factor necessary for the production of gangrene, which they consider to be the result of vascular obstruction secondary to inflammation or to embolism of the pulmonary artery. The papers of Kline (183, 184, 185) are based upon an entirely different conception of the nature of the two conditions and of their relations each to the other. Kline regards lung abscesses as essentially the result of pyogenic infection, usually staphylococcal and common in children, whereas gangrene is invariably the result of infection with spirilla and fusiform bacilli and is commoner in adults. He lays great stress upon this bacteriological distinction, which he considers to be of primary importance as regards both aetiology and treatment. D. T. Smith (316) considers the distinction between abscess and gangrene to be merely one of degree, a view put forward many years previously by Hutinel and Proust (162), and he prefers to prefix the term 'fuso-spirochaetal' to each type, hence differing from Kline, in that he recognizes the incidence of lung abscess due to fuso-spirochaetal infection. According to Smith, therefore, a localized

lesion is termed a 'fuso-spirochaetal abscess' and a larger lesion involving the greater part of a lobe is 'fuso-spirochaetal gangrene'; he recognizes, however, as a separate group the rare cases in which a similar gangrenous lesion may result from vascular obstruction.

Sée (307) was very sceptical as to the occurrence of lung abscess at all and stated that the incidence was so slight as to be almost negligible; he would only admit its presence on the post-mortem demonstration of a collection of pus in an area of grey hepatization. According to Aufrecht (9) a lung abscess is an infiltration of a piece of tissue with pus or white blood cells, which is followed by severance of its organic connexions with the surrounding tissue, and in this way the analogy between abscess formation in the lung and in the other tissues of the body is emphasized; although gangrene is discussed under a separate heading, no further definition of this term is given. Hartwell (136) defines lung abscess to be a collection of pus within destroyed lung parenchyma, and insists that the suppuration must occur outside the bronchial tree; the term 'gangrene' is reserved for a massive destruction of lung tissue which results either from gross vascular disturbance or from such an overwhelmingly virulent infection that the lung tissue is killed in mass either by toxins or by vascular plugging before there can occur a sufficient reaction to generate pus. Hartwell quotes Frost (107), who found abscess or gangrene in 148 cases in a series of 6,000 post-mortem examinations, and of these only seven conformed to the definition of pulmonary gangrene. Fischl (96) defines a true lung abscess to be an acute or sub-acute abscess which, not being preceded by other disease of the lungs, forms in the interalveolar connective tissues precisely as suppurative inflammations develop in the connective tissues of other organs. With this definition Bushnell (44) is in substantial agreement although he does not consider that the abscess necessarily arises without preceding disease of the lungs.

Sufficient evidence has been quoted to demonstrate the possibility of confusion arising when the views of various writers are compared, and much is therefore to be gained by employing only the simplest terms in the most comprehensive manner possible. For this reason the term 'gangrene' will not be employed in discussing the cases recorded in this series, and all cases of non-tuberculous cavitation with suppuration are included under the description of 'lung abscess'.

### *Classification*

The ideal classification of lung abscess should be easily applicable clinically, and should be so framed as to be helpful to those engaged in the management of these cases.

Since the use of X-rays and lipiodol has become almost universal in the investigation of chest diseases, it has been found possible to check the clinical observations at various stages of the disease, and thus individual cases may now be accurately assessed before the appropriate line of treatment is

finally selected. The basis of all clinical classifications, however, must eventually rest upon pathological studies combined with clinical observations, and it is hoped that the following simple anatomical scheme will be found useful in considering both the treatment and the mechanism of causation of lung abscesses.

### I. *Single.*

Unilocular Multilocular	$\left\{ \begin{array}{l} \text{Hilar} \\ \text{Central} \\ \text{Peripheral} \\ \text{Lobar} \end{array} \right\}$	(a) Open to	$\left\{ \begin{array}{l} \text{Bronchus} \\ \text{Pleura.} \end{array} \right\}$
		or	
		(b) Closed	

### II. *Multiple.*

Single abscesses vary greatly in size and in position, and those of small or moderate size are indicated in this scheme by a term which defines their position within the lung; the largest abscesses, which replace almost the whole of the affected lobe are not subject to variation in position, and the term 'lobar' is employed to indicate such cases.

Perhaps the earliest attempt at classification was that of Traube (332) who, in 1853, divided the types according to their origin, into abscesses arising from (i) blood-borne infections, (ii) infection conveyed through the bronchi, (iii) pre-existing lung disease. Although essentially accurate, this classification is of more value to the experimental pathologist than to the clinician. A very similar classification was propounded by Aschner (7) many years later, as the result of a study of lobes removed by Lilienthal at operation. Murphy (259) also formulated an aetiological classification, although on more elaborate lines, dividing his cases into the following groups: (i) acute circumscribed inflammation as occurs in pneumonic areas which have undergone necrosis and softening, (ii) peribronchitis, (iii) septic embolism of the pulmonary artery or of a single branch of the bronchial artery, (iv) rapid tuberculous caseation with secondary infection, (v) perforation of the lung by a malignant growth arising either in the oesophagus or in the mediastinum, (vi) subphrenic abscess perforating the lung, (vii) foreign body in the bronchus, (viii) infections following injury to the chest and, (ix) suppuration around a focus of malignant disease in the lung. He also added suppuration occurring in dermoid and hydatid cysts. Lilienthal (217) divides lung abscesses into two main types, which he terms 'interstitial' and 'bronchogenic'. The interstitial group includes cases due to injury, to blood-borne infection, and to lymph-borne infections; the bronchogenic cases consist of the aspiratory group of infections. Eggers (82) divides the cases into: (i) suppurations limited to, or originating in the bronchial tree, known as bronchiectasis, (ii) suppuration in the lung parenchyma, or true lung abscess, which he regards as being much less common, (iii) massive gangrene involving a large part of a lobe, which is probably always due to obstruction of a large blood-vessel by a septic embolus or thrombus. The second group is the only one in this classification which conforms to the definition accepted in this paper.

Ballon and Ballon (15) have studied the clinical aspect of the problem from a radiological point of view, and Ballon (14), following a study of the results of lipiodol injection, has elaborated a classification based upon the clinical and aetiological features of his cases, taken in conjunction with the radiological appearances. His classification, which is more detailed than the majority, is given in full.

*Group A. Solitary abscess.*

1. Single abscess with or without fluid level.
2. Bronchiectatic abscess, acute and chronic.
3. Abscess associated with bronchiectasis.

*Group B. Multiple abscesses* which may be associated with bronchiectasis.

*Group C. Abscess secondary to foreign body or to new growth.*

*Group D. Tuberculous abscess.*

While this classification is useful, the term 'bronchiectatic abscess' might lead to confusion, and it is open to objection on this account.

Kline and Berger (187) divide their cases into two groups, the single or aspiratory and the multiple or embolic abscesses. The French writers, notably Kindberg (181), Kourilsky (193), and Sergent (308), favour classifications based on bacteriology and although, in so far as certain infections may respond well to specific treatment, such classifications may have a limited value, yet for general purposes an anatomical or aetiological basis appears to be preferable.

*Aetiology.*

The majority of published series of cases are composed of material so selected as to exclude not only cases of multiple lung abscesses but also, in many instances, cases in which suppuration was due to the presence of certain specific lesions, such as neoplasms, in or near the main bronchi. This system of selection is justifiable in clinical series in which the effect of different methods of treatment is an integral and important part of the study, but it is not desirable in series which are concerned to any extent with a consideration of the aetiological factors involved in the production of pulmonary suppuration. In this section, all cases of pulmonary suppuration which conform to the definition given above have been included in two groups, (a) single abscesses, which include multiloculated cavities situated in a single lobe, and a few cases in which portions of adjacent lobes have been destroyed by the formation of a large cavity, and (b) multiple abscesses, in which group the remaining cases are included.

These two groups are considered separately in this section in order that the causal factors and the distribution may be compared. The results of this study will then be reviewed in their relation to other published series and also to the results of the experimental work which has been carried out in order to throw light on the genesis of the condition, for clinical and experimental studies must be considered in their relation to the anatomical

findings in the human subject before the theories and the facts can be arranged in their true perspective.

The present series consists of 315 cases, which were discovered in a study of the records of 11,006 consecutive post-mortem examinations. Every case in which the description was found to conform to the definition already given has been included and, in view of the heavy mortality which accompanies the treatment of lung abscess, whatever the cause, it may be claimed that the results are fairly representative of the aetiological factors commonly operative in this country.

The cases in the two groups will be considered separately and the causative factors will be subsequently compared.

*Single lung abscess.* Group I. 199 cases. Unilocular 149; multilocular 50.

Certain writers have claimed that lung abscess is becoming increasingly frequent. Whether this be a true increase in incidence or apparent, as the result of our very greatly increased facilities in diagnosis, it is not possible to determine. The factors which have to be considered in such an inquiry are so complex and so difficult to assess that no opinion can be usefully expressed on this subject.

*Sex.* The condition has always been reported as being considerably commoner in males in the proportion of 3 or 4 to each female. In this series 150 were male and 49 were female.

*Age.* The incidence appears to be spread over wide limits with a preponderance in middle age. The result is also in accordance with other published figures. The youngest case in this series died at the age of 22 days; the oldest at 78 years.

#### *Age Incidence*

Years.	Cases.	Years.	Cases.
0-9	28	40-49	43
10-19	18	50-59	35
20-29	15	60-69	35
30-39	19	70-79	6

That the heavier incidence in middle and later life is to some extent related to the incidence of malignant disease involving the respiratory tract will be appreciated by reference to Table I.

*Associated causal condition.* A very great variety of pathological states may lead to the formation of a lung abscess, and a full analysis of the apparent causes, as determined at autopsy in the present series, is given in Table I.

In some respects these associated causal conditions differ materially from those recorded by other workers, especially in the United States, and it is proposed, therefore, to proceed with the description of the actual findings in this series before attempting to consider their significance in their relation to other results.

TABLE I.

*Single Lung Abscess (199 cases)**Associated Causal Conditions**I. Lesions Involving the Respiratory Tract*

	Cases.
(a) <i>The Oropharynx:</i>	
Operation for carcinoma of tongue	2
Following tonsillectomy	2
Operation for carcinoma of tonsil	1
(b) <i>The Larynx:</i>	
Operation for carcinoma	2
(c) <i>The Trachea:</i>	
Tracheotomy (for catarrhal laryngitis 1, Innocent tumour of larynx 1, and carcinoma of larynx 1)	3
(d) <i>The Bronchi:</i>	
Foreign body	2
Bronchiectasis	2
Carcinoma	32
Perforating carcinoma of oesophagus	13
(e) <i>The Lungs:</i>	
Lobar pneumonia	19
Bronchopneumonia	24
Actinomycosis	2
Suppurating hydatid cyst	1
Secondary carcinoma (Breast 1, Rectum 1)	2
(f) <i>Chest Injuries and Operations:</i>	
Injury	2
Operation for empyema on opposite side	2

*II. Abdominal Conditions. Following operation for:—*

Subphrenic abscess	3
Perforated gastric and duodenal ulcer	7
Gastro-enterostomy	6
Gastrectomy	1
Bleeding gastric ulcer	1
Cholecystectomy	3
Appendix abscess	4
Umbilical hernia	1
Strangulated inguinal hernia	1
Carcinoma of colon	3
Hysterectomy	1
Radium to carcinoma of cervix	1
Operations on bladder and prostate	6

*III. Following Septic Conditions Elsewhere*

Cutaneous	4
Puerperal	4
Pneumococcal septicaemia	1
Osteomyelitis, 5, and septic arthritis 1	6
Otitis media	4
Lateral sinus thrombosis	3
Perinephric abscess	1

*IV. Lesions of the Central Nervous System*

Injury to skull or brain	3
Vascular lesion	1
Spinal injury	1

*V. Miscellaneous Causes*

Diabetes mellitus	2
Non-perforating carcinoma of oesophagus	3
Liver abscess (doubtful cause)	1

*VI. Cause Not Evident*

(Primary group)	16
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*Distribution.* A summary of the main distributional features is given in Table II, and these results may be compared with the findings of previous writers in order to show that the cases in this series were on the whole typical.

TABLE II  
*Distribution of Single Abscess*

<i>Right Lung.</i>	Cases.	<i>Left Lung.</i>	Cases.
Upper lobe	24	Upper lobe	17
Middle and upper lobes	5	Upper and lower lobes	6
Middle lobe	9	Lower lobe	53
Middle and lower lobes	6	Hilar	3
Lower lobe	74		
Hilar	2		
	<hr/> 120		<hr/> 79

Wessler (357) found that aspiratory abscesses were twice as common in the upper as in the lower lobes, and a similar distribution was reported by Flick, Clerf, Funk, and Farrell (99) and by Whittemore (363) and Fischer (95). Practically all the other series of any magnitude, however, have shown the reverse. Tuffier (336) stated that the lower lobes were involved in 80 per cent. of his cases and that the lesion was usually situated posteriorly. Moore (251) found the lower lobes involved in 60 per cent. of 202 cases of abscess following operation upon the respiratory tract. Lemon (206) compiled a comprehensive total which included his own cases, together with those of Walker (350), Wessler (357) and Norris and Landis (267), and he found that the lower lobes were involved twice as frequently as the upper, with which conclusion Davies (74) agrees.

The series reported by Hartwell (136), Lord (220), and Aschner (7) differ from the remainder in that the abscesses were fairly evenly distributed between the upper and the lower lobes.

There is general agreement, however, that the right lung is more commonly affected than the left, both in the series already quoted and in those published by Flick (98) and Kuelbs (198). These results may be compared with those of Babcock (10) who investigated the distribution of the lesions in 1,500 cases of lobar pneumonia, and found the right lung to be involved more commonly than the left and the right lower lobe to be affected in 33 per cent. of the cases.

In the present series, certain of the more important types of abscess, notably that following tonsillectomy, are very poorly represented, but an attempt has been made in Table III to convey a rough idea of the distribution of the main types in the proportions in which they affected the two lungs and their upper and lower halves.

A few cases in which the abscess was situated in the hilum, or in which more than one lobe was affected by a single abscess have been omitted in order to simplify the Table. Attention may be called to the preponderance of cases in which the right side and the lower lobes were involved, as has

been reported in the majority of published statistics. The cases which followed abdominal operations and peripheral infections, together with the primary group, all showed these characters to a greater or less extent; the pneumonic group showed a more even distribution, and the small group of cases in which there had been previous operative interference with the upper part of the respiratory tract proved exceptional in that the upper lobes were involved as frequently as the lower. It might have been expected from anatomical considerations that oesophageal carcinoma, especially in cases in which perforation of the trachea or of a main bronchus had occurred, would have caused lung abscess more frequently on the left side, yet the reverse proved to be the case and the right lower lobe was that most commonly affected.

TABLE III

*Distribution of Various Types of Single Abscess*

Cause of abscess.	Distribution.			
	Right lung.		Left lung.	
	Upper lobe.	Middle and lower lobes.	Upper lobe.	Lower lobe.
Lesions of mouth, larynx, and trachea (Ia, b, c)	3	3	2	1
Carcinoma of oesophagus (Id, and V)	3	9	1	2
Pneumonia and Broncho-pneumonia (Ie)	8	14	3	14
Abdominal operations (II)	1	25	1	10
Peripheral sepsis (III)	2	12	2	7
Primary (VI)	1	6	1	4

In this connexion, it may be appropriate to consider at this stage, observations which have been made on the distribution of emboli within the lungs. Capelle (48) studied 15 cases of massive pulmonary infarction occurring in a series of 10,000 operations and found that 13 emboli lodged in the lower lobes, and that the left side was affected in two cases only. Cutler, in a series of 40 cases, found the right side involved in 27 and the left side in 10, the remainder being bilateral; the lower lobes were more commonly affected than the upper in the proportion of 34 to 4. Welch (355), many years previously, reached a similar conclusion and summarized the factors involved by stating that the course followed by an embolus is determined by purely mechanical factors, of which the most important are the size, form, and weight of the plug, the direction and volume of the blood-stream, the size of the vessels, and the angle at which they are given off from the main stem, and the position of the body when the embolus was dislodged.

It would seem, therefore, that emboli show a predilection for the right side and the lower lobe, and this arrangement is so similar to that which results from the aspiration of foreign material that no conclusion can be drawn from the position of a lung abscess as to its mode of origin. On the other hand, it seems highly probable that abscesses which are situated near

the periphery of the lung are embolic in origin, and conversely that, the nearer the abscess is to the hilum, the more likely is it to result from aspiration. The larger abscesses which occupied the major portion of a lobe have been classed separately as it is usually impossible to determine whether they originated at the periphery or deep in the substance of the lobe, although the latter is the more probable, and abscesses situated at the extreme base of the lung are classed separately, as these are not peripheral in quite the same sense as are the others; the distribution of the abscesses was as follows:

	Right lung.			Left lung.	
	Upper lobe.	Middle lobe.	Lower lobe.	Upper lobe.	Lower lobe.
Central	2	0	13	5	10
Peripheral	12	6	23	7	16
Basal	0	0	20	0	12
Lobar	8	3	6	3	13

In eighteen cases the notes were not sufficiently clear to enable the site of the lesion to be determined with certainty. Abscesses situated in the hilum of the lung and abscesses which involved more than one lobe are not included in this summary. The majority of the lesions were situated at the periphery of the lung, many of these in contact with the visceral pleura, and their situation tends to suggest that embolism rather than aspiration was the commoner cause. The cases are further analysed in Table IV, in which is shown the distribution of those lesions due to the commoner aetiological factors.

TABLE IV

*Distribution of Certain Types of Single Abscess*

Cause of abscess.	Central.	Lobar.	Peripheral.	Basal.
Lesions of mouth, larynx, and trachea (I a, b, c)	2	0	3	4
Pneumonia and Broncho-pneumonia (I e)	14	6	17	2
Abdominal operations (II)	4	6	7	20
Peripheral sepsis (III)	1	1	18	1
Primary (VI)	3	2	5	2

Although the inferences to be drawn from a study of the distribution of the lesions are not conclusive, yet it is clear that the abscesses which resulted from sepsis elsewhere in the body and were, in fact, embolic in origin were distributed chiefly at the periphery of the lung, especially in the lower lobes, whereas those abscesses which resulted from operative interference with the upper part of the respiratory tract, and were presumably aspiratory, had a slightly different distribution, chiefly at the base of the lung. It would seem, therefore, that a guide as to the causation of the post tonsillectomy lung abscess might be obtained by the study of a series of cases of this type from the point of view of their distribution; there does not appear to have been any careful study of the subject in this respect.

The fact that pneumonic and primary abscesses were distributed fairly evenly throughout the lung tissue tends to suggest that these types may have a common origin. The cases which followed abdominal operation occurred almost entirely in the lower lobes and chiefly at the base, thus resembling the aspiratory group; this observation may, however, be fallacious, for evidence will be quoted in a later section to show that the abscess which follows an abdominal operation is not commonly aspiratory in origin.

*Associated changes in the lungs.* The state of the lungs, apart from the actual abscess cavity deserves consideration, in that the decision as to which method of treatment should be adopted in any individual case may depend upon the conception of the changes which are expected to be present elsewhere in the chest. The section which deals with the associated causal condition conveys some information as to other conditions which were present in the lungs in certain of the cases, but in addition other changes were found.

In the primary group there was considerable recent broncho-pneumonia surrounding the abscess in 5 out of the 16 cases; in the remainder, there was no recent inflammatory lesion beyond the immediate wall of the cavity. The lung tissue was collapsed in 4 cases, in each of which much fluid was present in the pleural sac. In one of the more chronic cases there was a marked fibrous tissue reaction in the area of lung surrounding the lesion and in another the abscess had originated in a previously fibrosed lobe. Bronchiectasis, of a mild tubular type was present in one case, distal to the abscess, and consequent upon it.

The pneumonic groups consisted of 43 cases in all, and in the majority of these the abscess had resulted from the breaking down of a portion of the consolidated lung. Pneumonic changes were present in lobes other than that which contained the abscess in 15 cases, of which 5 had a lobar and 10 a broncho-pneumonic distribution. Lobar pneumonia was present as an additional feature only in cases in which the same condition had caused the lung abscess, but broncho-pneumonia was present in other lobes in 2 cases in which the abscess had resulted from lobar pneumonia. Mild bronchiectasis was present in 3 cases and a considerable degree of pulmonary fibrosis in 1; in each of these the bronchial lesion appeared to have antedated the pneumonia.

The embolic group, which consisted of 23 cases, exhibited marked acute broncho-pneumonia in 11 cases, and in 6 others recent pulmonary infarcts were present. In only 1 case were infarcts and a significant degree of broncho-pneumonia present together.

The cases in which lung abscesses occurred as a complication of abdominal operation, 38 in all, showed broncho-pneumonia in 16, lobar pneumonia in 2, and obvious infarction on 1 occasion only. Evidence of an antecedent chronic pulmonary lesion, a mild basal bronchiectasis, was found in 1 case. In the group of 10 cases in which the condition resulted from operative interference

in the upper respiratory tract, broncho-pneumonia was present in 5 cases and there was no evidence of infarction.

The complications of bronchial carcinoma have been dealt with in many papers and are of little significance so far as a study of lung abscess is concerned, so that they need not be considered. In the remaining groups, broncho-pneumonia was present in 4 cases.

*Other pulmonary conditions.* Gross terminal oedema of the lungs was present in 18 cases altogether, and congestion with slight oedema in the majority.

There was very little evidence of chronic pulmonary disease. Fibroid and calcareous tuberculous lesions were present in 9 cases and a simple fibrosis in 2 others. Apart from these changes, the general state of the lungs does not appear to have been worthy of comment in the post-mortem records.

TABLE V  
*The Pleura*

	Cases.
<i>Normal</i>	10
<i>Adhesions</i>	
(a) <i>Old and dense:</i>	
In the region of the abscess	35
Away from the abscess	3
Generalized	25
(b) <i>Recent pleurisy with fibrinous adhesions:</i>	
In the region of the abscess	31
Away from the abscess	3
Generalized	10
<i>Pleural Effusion</i>	
Clear fluid	4
Turbid fluid	3
Empyema	46
Pyo-pneumothorax	5
Haemopneumothorax	1
Blood-stained fluid	1
<i>Miscellaneous Conditions</i>	
Infiltration with new growth	3
Miliary tubercles	1
<i>No note in</i>	18
<i>Empyema on the opposite side</i>	11

*Associated changes in the pleura.* The state of the pleura is of fundamental importance from the point of view of treatment, especially in cases in which operation or collapse therapy have to be considered. In this series, which consists to a large extent of cases unsuccessfully treated, it must be remembered that some of the more recent inflammatory changes may have been initiated or aggravated by therapeutic interference, although it is not possible accurately to assess this factor. Operations had been performed on the chest in 19 cases, in 9 of which rib resection had been carried out for the drainage of empyema, in 5 the abscess cavity had been opened, and in 5 an exploration of the chest had been undertaken for diagnostic purposes. The condition of the pleural cavity is summarized in Table V.

As might be expected, a normal pleural cavity was rarely found, yet for

the purposes of collapse therapy, any gross abnormality renders the induction of a pneumothorax either impossible or dangerous. In 2 of the cases in which pyo-pneumothorax was present, an artificial pneumothorax had been recently induced.

Comparatively little attention has been paid in the literature to the state of the pleura in cases of lung abscess. Eggers (81) reported 10 cases in which the abscess had perforated the pleural cavity, with recovery after drainage in every case; he therefore regards extension to the pleura, particularly if it occurs slowly, as a good prognostic sign. Lockwood (218) stated that pleural adhesions are present in the majority of cases, Picot (275) noted their presence in 53 per cent. of 149 cases, Tuffier (336) in 87 per cent. of his series and McRae (233) in a series of 75 cases found adhesions present in 85 per cent. of the acute cases and in 81.3 per cent. of all cases. Korte (192), in a series of 37 cases noted the presence of empyema in 8, and of these no less than 7 terminated fatally. Heuer and MacCready (147) encountered empyema in 12 out of 62 cases and Fraenkel (103) in 11.8 per cent. of a series of 85 cases. Wilensky (366), in discussing 88 cases of empyema, concluded that practically all were secondary to some inflammatory lesion within the lung; thus the obscure empyema which does not follow a frank pneumonia is often secondary to a small lung abscess, which may easily be overlooked unless a careful search be made. Lord (221) found adhesions over the surface of a lung abscess in 30 out of 35 cases examined *post mortem*, although in only 12 cases were the adhesions described as dense.

No further comment is needed on these figures at present, but their significance in connexion with the choice of treatment is obvious.

*Changes elsewhere in the body.* In many cases there were lesions present in other parts of the body which were also secondary to the lesion which caused the lung abscess, as, for instance, suppurative pyelonephritis following prostatectomy. Such conditions are not included in this discussion unless they might be considered to have some bearing upon the cause of the lung abscess.

The following were the chief changes found elsewhere than in the respiratory tract.

1. *Heart.* Acute pericarditis was present in 15 cases, and the infection had attacked the heart valves in no less than 11, in addition to which the wall of the right auricle contained an adherent septic thrombus in 1 case. The distribution of the lesions upon the valves were as follows:—

Aortic in 2 cases.

Mitral in 3 cases.

Mitral and aortic in 1 case.

Mitral and tricuspid in 1 case.

Pulmonary in 4 cases.

Thus there was gross infection on the right side of the heart in 6 cases.

2. *Nervous System.* Acute meningitis was present in 9 cases and cerebral abscess in 4, an incidence of only 2 per cent. It is interesting to note that

in three out of these four cases an empyema was present, and experience of other cases suggests that cerebral abscess is a much commoner complication of combined pulmonary and pleural sepsis than it is when either condition exists alone.

The incidence of cerebral abscess is variously reported. Tuffier is quoted by Sauerbruch (297) as stating that the incidence of this complication is 13 per cent., and Hamman regards it as being relatively common and states that the cerebral lesions are often multiple, as occurred in two out of four cases in this series. Martius (239), in 1891, recorded 22 cases observed at autopsy, and Cameron (46), in 1907, described 17 further cases. There were three cases in Lockwood's series, of which one recovered.

3. *Abdomen.* It has been claimed by the exponents of the embolic theory that lung abscess following abdominal operations is the result of septic pulmonary infarction. A study of local conditions reveals that, out of 38 cases in which an abdominal operation had been recently performed, there was gross sepsis at the operative sight in no less than 29, and of the remaining 9 in which the local abdominal condition was apparently clean, the pulmonary condition was suggestive of broncho-pneumonia in 5, diabetes with broncho-pneumonia was present in 1, a septic femoral venous thrombosis in 1, and in the remaining case the condition was described as a breaking-down infarct.

Subphrenic abscess was present in 6 cases, in 4 of which there was an obvious trans-diaphragmatic communication between the two abscess cavities, and gross hepatic suppuration was present in 6 other cases, in only one of which could a communication be discovered.

Liver abscesses were present in 10 cases altogether, and abscesses were found twice in the spleen and eight times in the kidneys.

4. *Miscellaneous.* Scattered abscesses in joints, muscles, and subcutaneous tissues were present in three cases. In addition, primary carcinoma of the stomach was present in a case in which the lung abscess had resulted from obstruction of the bronchus as a result of a second primary growth in that situation and in two cases in which lung abscess had followed closely upon operation for prostatectomy, and which are included in the tables under that heading, early malignant disease of the bronchus and of the oesophagus were present respectively, although the latter condition probably played no part in the development of the abscess.

In 3 cases the abscess had occurred in patients suffering from diabetes mellitus.

#### *Multiple Lung Abscesses*

In most series the group of multiple abscesses is purposely omitted, particularly as treatment is unlikely to be effective in this type of case. Yet by a comparison of the aetiological factors involved in the two types, information as to the mode of production of the single abscess may be obtained, and a brief summary of the chief aetiological points in this group will therefore be given.

*Multiple abscesses.* Group II. 116 cases.

*Sex.* There were 82 males and 34 females, the preponderance of males being slightly less in this group.

<i>Age.</i>	<i>Cases.</i>		<i>Cases.</i>	
	0-9	26	40-49	21
	10-19	16	50-59	14
	20-29	14	60-69	6
	30-39	18	70-79	1

TABLE VI.

*Multiple Lung Abscesses (116 Cases)*

*I. Lesions Involving the Respiratory Tract*

(a) <i>The Oropharynx:</i>	<i>Cases.</i>
Operation for carcinoma of tongue	1
" " retropharyngeal abscess	1
(b) <i>The Larynx:</i>	
Ulceration	1
(c) <i>The Trachea:</i>	
Tracheotomy (for laryngeal obstruction —1, for carcinoma of larynx —1)	2
(d) <i>The Bronchi:</i>	
Bronchiectasis	10
Carcinoma	2
Perforating carcinoma of oesophagus	3
(e) <i>The Lungs:</i>	
Broncho-pneumonia	6
Actinomycosis	2
Aspergillus infection	1
Gummata	1

*II. Abdominal Conditions. Following operations for:—*

Perforated gastric and duodenal ulcer	3
Gastro-enterostomy	1
Appendix abscess	1
Strangulated femoral hernia	1
Carcinoma of rectum (insertion of radon)	1
Oophorectomy	1
Prostatectomy	1

*III. Following Septic Conditions Elsewhere*

Acute osteomyelitis	21
Acute septic arthritis	3
Cutaneous and subcutaneous sepsis	17
Puerperal	5
Nasal sinusitis	2
Otitis media	5
Mastoid operations	6
Pyorrhoea	1
Operation for stricture of urethra	2

*IV. Lesions of the Central Nervous System*

Vascular lesions	2
Operations on skull and brain	2

*V. Non-perforating Carcinoma of Oesophagus* 4

*VI. Cause Not Evident*

'Cryptic'	7
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Again, the incidence is spread comparatively evenly over a wide age period, yet the preponderance is on the whole on the side of youth in comparison with the previous group, and this is to some extent in agreement with the observations of Kline (184).

*Associated causal condition.* For the purpose of comparison the causes of multiple lung abscesses have been detailed in Table VI, which is arranged, as far as possible, to correspond with Table I.

TABLE VII  
*Causation of Single and Multiple Lung Abscesses*

Cause.	Single.		Multiple.	
	Cases.	%.	Cases.	%.
Lesions of the upper respiratory tract (I a, b, c)	10	5	5	4.3
Bronchial carcinoma	32	16	2	1.7
Carcinoma of oesophagus	16	8	7	6
Acute pulmonary inflammations	43	21.5	6	5.2
Abdominal operations	38	19	9	7.8
Septic conditions elsewhere :—				
Cutaneous	4	2	17	14.7
Puerperal	4	2	5	4.3
Bones and joints	6	3	21	18.1
Ear disease	7	3.5	11	9.5
Primary (or cryptic)	16	8	7	6

A few points call for comment when these aetiological factors are compared with those which are detailed in the case of single lung abscess, and in order to facilitate comparison, the causal factors in the two groups are contrasted in Table VII. Septic conditions of the upper part of the respiratory tract are not a conspicuous feature of either table, and they appear to be about equally liable to cause local or diffuse pulmonary suppuration. Bronchial carcinoma almost always causes local abscess, whereas with bronchiectasis multiple foci are much more frequently found. The pneumonic cases usually form a single abscess.

Multiple abscesses are considerably less frequent than the single variety following abdominal operations, but it may be noted that in each of the nine cases in this group there was evidence of gross infection at the site of the operation.

The great majority of the cases in this group are seen to have occurred as a complication of a peripheral septic focus, most commonly situated in connexion with bone or with the skin. In these cases it is difficult to imagine that the pulmonary condition could result otherwise than from embolism.

Finally, attention must be called to the group styled 'Cryptic'. In these cases there were multiple abscesses similar in all respects to those which occurred as the sequelae of peripheral sepsis, in none of which could any primary focus be discovered. The incidence, 7 out of 116 cases, was somewhat similar to that of the primary group of single abscesses, 16 out of 199

cases, a point which raises the speculation as to whether each group may not owe its origin to embolism from some cryptic focus of peripheral infection. These cases in which multiple abscess formation occurs do not present so distinct a clinical picture as do the primary cases of solitary abscess, yet, in considering a series of cases, the type emerges as a pathological entity quite as clearly as does the corresponding group of primary lung abscess.

*Distribution.* It is much more difficult to convey an impression of the distribution of multiple lung abscesses than of the single variety, but the position is stated as clearly as possible in Table VIII.

TABLE VIII  
*Distribution of Multiple Lung Abscesses*

	Cases.		Cases.
Both lungs equally	60	Both upper lobes	2
Both lungs—chiefly right	3	Both lower lobes	11
Both lungs—chiefly left	6	Right lung and left lower lobe	4
Right lung	17	Right upper and left lower lobe	1
Right middle and lower lobes	2	Right lower and left upper lobe	1
Left lung	9		

It can be seen that neither side can claim a preponderance of the lesions, which appeared for the most part to be symmetrical. Although it is not possible to convey any more accurate idea of the situation of the lesions, it may be stated that the great majority were situated peripherally, and that the lower lobes contained many more abscesses than the upper as a rule.

*Associated changes in the lungs.* It is difficult and not very important to consider the associated pulmonary changes in detail, and only the main abnormalities will be enumerated. Secondary broncho-pneumonia was present in 28 cases, and old-standing tubular bronchiectasis in 8; typical infarcts were noted in 15 instances in association with the lung abscesses.

*Associated changes in the pleura.* As the lung lesions were bilateral in the majority of cases, only the main abnormalities are noted:—

	Cases.
Empyema . . . . .	30
Acute pleurisy . . . . .	29
Pyo-pneumothorax . . . . .	5
Clear effusion . . . . .	4
Old adhesions . . . . .	30
No abnormality . . . . .	3

The incidence of septic pleural complications is thus seen to be rather higher with multiple than with single abscesses, a fact which will be readily understood when the higher incidence of subpleural pulmonary lesions is considered.

*Changes elsewhere in the body.* The extrapulmonary changes were chiefly pyaemic, as would be expected, and may be compared with the previous group.

	Cases.
Abscesses in the heart wall. . . . .	10
Suppurative pericarditis . . . . .	12
Septic endocarditis (tricuspid 2, mitral 1) . . . . .	3
Cerebral abscesses . . . . .	1
Suppurative meningitis . . . . .	2
Abscesses in kidneys . . . . .	18
Perinephric abscesses . . . . .	2
Splenic abscesses . . . . .	4
Liver abscesses . . . . .	7
Subcutaneous abscesses . . . . .	5
Intramuscular abscesses . . . . .	3
Metastatic bone abscesses . . . . .	6

In addition, diphtheria was present in one case, and the septic condition was a terminal event in diabetes on one occasion.

### Bacteriology

The bacteria which were found to be present in these cases were varied, but, as all the material from which this paper is derived was obtained *post mortem*, and as reports were not furnished in every case, the results of the bacteriological study cannot be termed conclusive. Nevertheless, a certain amount of information can be obtained as to the relative frequency with which the commoner organisms were found, by a consideration of the results of the examination of material from the local lesions and also from the heart's blood, and the results are summarized in Table IX.

TABLE IX  
*Bacteriology of Lung Abscess*

	Single abscess.		Multiple abscesses.	
	Heart's blood.	Local lesions.	Heart's blood.	Local lesions.
<i>Staphylococcus aureus</i>	14	4	31	9
<i>Staphylococcus albus</i>	1	0	2	0
Streptococci (non-haemolytic)	10	2	2	0
Streptococci (haemolytic)	2	0	1	0
Pneumococci	10	4	1	0
<i>B. Pfeiffer</i>	1	3	0	0
<i>B. Friedlander</i>	0	1	0	0
<i>B. coli</i>	4	2	0	0
<i>B. Welchii</i>	0	1	0	0

The proportion in which bacteriological investigations were made is not great, for records were only preserved in 105 out of 315 cases, nor is the presence of organisms in the heart's blood conclusive evidence that the lung abscess was the result of an infected embolus in any given case, yet these results may have some significance when they are correlated with the anatomical changes already detailed.

A great number of observations, experimental, clinical, and pathological, have been made by numerous workers who have studied the bacteriology of lung abscess. The earliest recorded bacteriological study is that of Leyden and Jaffe (211), who, in 1867, first discovered spirilla in the sputum obtained from cases of bronchiectasis and lung abscess. In 1895 Babès (11) expressed the view that, although saprophytic organisms alone cannot cause pulmonary suppuration, yet they nearly always occur in such cases in association with organisms of recognized pathogenic properties; in 24 cases, staphylococci were present in 12, streptococci in 12, and virulent pneumococci in 3, together with diphtheroid bacilli in 10 cases altogether. Three years later Withington (371), however, reached the conclusion that certain organisms which are normally saprophytic may at times be the cause of pulmonary suppuration. In 1902, Ophuls (269) described acid-fast bacilli, allied to, but distinct from, tubercle bacilli in 5 cases; these organisms have been apparently not been found by other observers.

The part played by the pneumococcus has been the subject of considerable discussion. In the earlier years of the present century lung abscess was commonly considered to be a relatively common sequel of pneumonic conditions, and the pneumococcus was assumed, therefore, to be the cause of the condition, but with the advance of bacteriological technique and the concentration of attention upon other supposedly specific organisms, the part played by the pneumococcus has been considered to be less important. In 1911 Guinon (128) described a case of lung abscess in a congenital syphilitic boy, in which the virulence of the organism was proved by injection into a mouse, and in 1913 Barrington-Ward (17) described a similar case; the latter writer divided pneumococcal abscesses into three types, those following the inhalation of a foreign body, multiple abscesses in broncho-pneumonia, and single abscess which might complicate lobar pneumonia or might arise as a primary condition. Nobécourt (265) has recently described a case of acute pneumococcal abscess with recovery.

Other organisms which are commonly found in the respiratory tract have been described as the cause of lung abscess in occasional cases. Hitzig (150) found *B. Pfeiffer* repeatedly in the sputum of one case, and Belk (21) and Kornblum (191) have described lung abscess due to infection with Friedlander's bacillus; in this condition the sputum is apparently never foul.

The part played by streptococci in the causation of lung abscess does not appear to have been extensively studied. In a careful investigation of the bacteriology in 118 cases, using pus collected through a bronchoscope, Bucher (38) found streptococci, mostly of the viridans type, in no less than 93, and in fact these were by far the most constant organisms present. He found that several varieties of the organisms were usually present together and concluded that no single organism can be regarded as the cause of the condition, but he also noted that the bacteria present were those commonly found in the mouth. Pilot and Davis (277) also considered that streptococci played an important contributory role in the causation of the condition.

It has already been stated that Kline (183, 185) regards true lung abscess as a condition caused by infection by pyogenic organisms, usually staphylococci, but his terminology depends largely on the bacteriological findings. Kline and Berger (187) point out that pus in abscesses caused by the pyogenic cocci is odourless, in distinction to that which results from anaerobic infection, but Hartwell (136), who also regards the staphylococcus as a potent cause of lung abscess, considers that the odour of the pus is no true guide in the distinction between abscess and gangrene. Ermatinger (86) studied a series of 16 cases and found *Staphylococcus aureus* as the predominant organism in 13, but the infection was always mixed, and haemolytic streptococci were also present in 11 cases. Lockwood (218) regards staphylococci as being commonly associated organisms although he also considers that streptococci, usually non-haemolytic, and *B. influenzae* are important organisms in the group which complicates pneumonia. Greer (124) found staphylococci in the majority of a series of 33 cases.

The role of anaerobic organisms has engaged increasing attention from the time of Leyden and Jaffe to the present day. In 1898 Veillon and Zuber (345) were perhaps the first to attach significance to the presence of anaerobes in pus derived from the abscess, and in 1905 Rona (293) reported the presence of spirochaetes in cases of pulmonary gangrene. In the following year Castellani (50) reported the presence of spirochaetes in the sputum of two cases of 'haemorrhagic bronchitis' in Ceylon, and within the next few years cases of spirochaetal broncho-pulmonary infection were also recorded by Rothwell (294), who reported two cases of bronchial Vincent's angina, Buday (39), who found spirochaetes and fusiform bacilli in the majority of his cases of gangrenous abscess, Peters (273), Dick (77), and others. In 1918 Thomson (329), Paraf (272), and Weil (354), and in 1920 Nolf (266) published further reports and Rawson (285) reported a case of spirochaetal lung abscess four years later. In 1924 Pilot and Davis (277) published a study of 37 cases of fuso-spirochaetal lesions of the lungs and considered that this type of infection should be classed as a distinct clinical entity, although they recognized that the pyogenic organisms played an important contributory role; they included in their paper a careful study of the organisms present in dental tartar and in the tonsils, and they pointed out that the organisms discovered in the mouths of many normal persons are identical with those which they found in mild cases of pulmonary suppuration. In the same year Lambert and Miller (202) reported 10 cases, in each of which anaerobic organisms were present in the pus taken from the abscess; the organisms found included *Streptothrix* (6 cases), Gram-positive cocci (6 cases), Gram-positive bacilli (4 cases), Gram-negative bacilli (7 cases), fusiform bacilli (2 cases) and spirilla in one case only. In 1926 Bezançon and Etchegoin (28) recorded cases of fuso-spirochaetal pulmonary disease, and in 1929, Lambert and Weeks (203) stated that many abscesses contained anaerobes only and that these organisms are pathogenic for dogs. About the same time Kline and Berger (187) identified the organisms present in gangrenous lung lesions

with oral spirochaetes and Flick, Clerf, Funk, and Farrell (99) stated that spirochaetes and fusiform bacilli were commonly present in their series of 172 cases. Recently Kline (185) has amplified his view, already mentioned, that the lesion which he terms 'gangrene' is spirochaetal in origin and his paper contains a discussion and criticism of contemporary experimental work. Heuer (146) considers that anaerobic mouth organisms are present in about 75 per cent. of cases of lung abscess, and Pinchin and Morlock (278) state that spirochaetes and fusiform bacilli were present in 8 of their 27 cases.

The work of Smith (313, 314, 315, 316) must be considered separately on account of his numerous papers and dogmatic views upon the part played by fusiform bacilli and spirilla in the causation of lung abscess. He considers that the distinction between fuso-spirochaetal abscess and gangrene is merely one of degree and prefers to use the term 'abscess' for the more definitely localized lesions. He states that pulmonary gangrene is always fuso-spirochaetal except in rare cases of infection with spore-bearing anaerobes in cases where the blood supply of a considerable part of the lung is interrupted. He quotes Kline and Berger (187) to the effect the 90 per cent. of all abscesses in adults and 50 per cent. in children are fuso-spirochaetal, the remainder being chiefly staphylococcal, and he mentions streptococci, *B. Friedlander*, *B. coli*, and *Actinomyces* as occasional causal organisms. It is not clear from any of his papers, however, that the fusiform bacilli and spirochaetes were the actual cause of the lung abscesses and not secondary invaders. According to Smith, pneumococcal infections do not predispose to pulmonary suppuration. In temperate zones the spirochaetes are always associated with fusiform bacilli, although this is not necessarily the case in the tropics. Smith concludes that since the war, it has been recognized that fuso-spirochaetal infection is very common, ranking next to tubercle as a cause of chronic pulmonary disease, and he has collected a series of 2,255 cases reported in the American literature up to 1932.

From the purely bacteriological point of view Tunnicliff (337, 338) has studied the fusiform bacilli and spirochaetes, and she concludes that the two organisms are in reality identical.

In rare cases other organisms have been described as the cause of lung abscess. Clauberg (58) and Lilienthal (213) have each reported a case occurring in the course of a paratyphoid infection. Delmas and Duhamel (75) encountered a similar case in the course of Malta fever; and amoebic lung infection has been recorded by Harrington (134) and by Rist (291).

Varney (344) discussed the bacteriology of 27 cases, 21 of which had not been previously treated, and he found that the predominant organisms were streptococci, usually non-haemolytic, fusiform bacilli, spirochaetes and *B. melaninogenicum*, and he also drew attention to the remarkable similarity of these findings to the results of the examination of diseased teeth. Guillemot (127) found a variety of organisms, of which he regarded *B. ramosus* as the most important.

The whole subject of the bacteriology of lung abscess is very complicated and, as can be seen from the foregoing summary, very diverse findings have been recorded. These discrepant results are perhaps due partly to variations in bacteriological technique. The subject has been reviewed from all points of view by Smith (316), Cohen (64), Arnheim (6), Lockwood (218), and by Marshall and Brunn (238). The latter conclude that there is no reason to suppose that one single organism is responsible, and that it seems probable that *B. fusiformis* is a secondary invader of tissues already diseased or devitalized; there is very little doubt, that this organism helps to maintain or to further the progress of gangrenous conditions.

The varied reports of the bacteriological findings in cases of lung abscess may be partly due to differences in the routine methods of examination employed in different clinics, and it certainly appears that spirochaetes and fusiform bacilli are likely to be overlooked unless specifically sought; in the cases described here spirochaetes were not reported on any occasion, probably for this reason.

The great majority of writers agree that lung abscess may result from infection with one or more of a variety of organisms, and there is no reason to doubt this conclusion. Nor is the specificity of the spirochaetes and other anaerobic organisms conclusively proved, although these appear to be frequently present.

#### *Discussion on Aetiology*

The literature dealing with the causation of lung abscess can be sharply divided into two periods, that of more than twenty years ago being concerned with such factors as pneumonia and other local inflammatory conditions, whereas more recently chief attention has been focused upon pulmonary *sequelae* of operation in the mouth and throat. In consequence of the importance attached to the latter factors by present day writers these will be considered in the first place.

*Tonsil operations.* It is usually stated that Richardson (287) and Bassin (20), in 1913, were the first to describe lung abscess as a sequel of tonsillectomy, as they certainly were the first to ascribe to it the importance which it has since been recognized to possess, yet Le Play (209) had recognized the condition in 1905, and in 1911 Grossard and Kauffman (126) had described certain pulmonary sequelae of tonsillectomy, and among them a case of 'foetid bronchitis' which proved fatal after lasting for a year, and which was very probably a lung abscess. Richardson described two cases, both of which eventually recovered, and he evidently regarded the lesions as embolic, for he described them under the heading of pulmonary infarcts, and in his second paper (288) speaks of septic infarct of the lung, although some years later he considered the aspiratory theory 'hardly open to argument' (289). Bassin described 16 similar cases. Some years later Wessler (357) estimated that 28 per cent. of the pulmonary operations passing through the X-ray

department of the Mount Sinai Hospital, resulted from tonsillectomy, and in 1916 Manges (236) reported 9 cases seen in the course of a single year and commented upon the fact that this complication occurred as a rule when the operation had been performed with the patient in an upright position. He, therefore, with Coakley (63) considered that the complication resulted from the aspiration of septic blood-clot or of actual particles of infected tonsillar tissue, whereas Yankauer (372) considered that the presence of gaping veins in the tonsillar bed supported the alternative hypothesis of septic pulmonary infarction. In the next few years papers were published with increasing frequency. In 1917 Frank (104) reported 3 cases, and in 1918 Bevan (30) stated that he regarded lung abscess as an important sequel of tonsillectomy; in the following year Pottenger (280) published a series of 20 cases encountered within eighteen months, and in 1921 Keiper (177) reported one case, Whittemore (362) reported a series of 32 cases of lung abscess, 17 of which followed tonsillectomy, and Fisher and Cohen (97) reported 5 cases of their own and discussed a further 71 which they had collected from the literature. In 1922 Moore (251) published an analysis of 202 cases of lung abscess which had occurred in approximately 450,000 operations upon the upper respiratory tract and concluded that this complication occurred about once in 2,500 operations; it may be noted that local anaesthesia was employed in 19.3 per cent. of this series. Lockwood (218) also recognized the frequency with which lung abscess occurred after tonsillectomy in the United States and reviewed the literature fully. In 1923 Glowacki (112) estimated that lung abscess occurred as frequently as once in 358 tonsillectomies, the most extreme figure recorded. Mackenzie (231) reported 169 cases in 1924, 11 of which followed tonsillectomy, and Hedblom (140) reported 692 cases in the same year, of which 146 were post-operative; of the latter group 47 cases (31 per cent.) followed tonsillectomy and 14 (9.5 per cent.) followed dental extraction. The great majority of these operations were performed under general anaesthesia, whereas, in a series of 16,000 tonsillectomies performed under local anaesthesia at the Mayo Clinic, there were only two cases of lung abscess. The influence of the type of anaesthesia upon the incidence of lung abscess has been very variously estimated. In addition to the figures of Moore and of Hedblom, already quoted, Lockwood (219) found that, of 208 cases of lung abscess following tonsillectomy only 7 operations were performed under local anaesthesia, and in 25,000 tonsillectomies performed under local anaesthesia at the Mayo Clinic, there was only one lung abscess, which was clearly pyaemic in origin. Ascoli and Boniades (8) consider that 50 per cent. of all lung abscesses in the United States follow tonsillectomy and they state that, in Italy, where operations upon the tonsils are nearly always performed under local anaesthesia, this variety of abscess is almost unknown. Holman (154) found that the average period required for the development of the abscess was six days, no matter whether a general (187 cases) or a local anaesthetic (34 cases) was employed, and he regarded this finding as an argument in favour of embolism

and against aspiration which, he considered, would be expected to show a shorter incubation period.

Lord (223) studied a series of 227 cases of which 78 followed operations upon the upper respiratory tract, tonsillectomy in 49 cases and dental extractions in 21 cases. In 1928 Crowe and Scarff (68) recorded a series of 3,500 cases in which tonsillectomy had been performed without misadventure under ether anaesthesia after very careful precautions had been adopted to prevent any inhalation of foreign material, and they regarded this result as a point in favour of the aspiratory theory. It must be noted, however, that Moore's larger series shows an average incidence of one case of lung abscess in 2,500 tonsillectomies, so that the series of Crowe and Scarff is much too small to permit definite conclusions to be drawn; recently Wirth and Renno (370) have recorded the complications in their series of 2,766 cases in which tonsillectomy was performed and lung abscess did not occur, although apparently no special precautions were adopted to prevent aspiration. Fischer (95) pointed out that lung abscess is a much more common sequel of tonsil operations in adults than in children, and the subject has also been discussed by Wall (351), Miller (244), Gatewood (110), and by many others. Flick, Clerf, Funk, and Farrell (99) described 172 cases of which 121 followed operations, tonsillectomy accounting for 97 and other mouth operations of 10 cases; local anaesthesia was employed on four occasions only. Schlueter and Weidlein (303) have summarized a series of 1,908 cases of which 515 followed operations, 278, or 14.6 per cent. of these being tonsillectomies. More recently Yates (376) has discussed 4 cases, 2 of which followed tonsillectomy, and further recent observations have been published by Leukowitz (210) and by Frank (105).

In this country Pinchin and Morlock (278) found that tonsillectomy accounted for 16 per cent. of their cases of lung abscess.

As compared with the figures already quoted, the incidence of lung abscess following mouth and throat operations in the series described in this paper appears to be extremely low. The cases have been derived from a large general hospital and from a special chest hospital, and it may therefore be assumed that they represent a fair sample of the incidence of the condition when fatal cases are being considered. A low incidence has also been found in certain other series, notably that of Lyman (226) who reported 20,000 cases of tonsillectomy under nitrous oxide anaesthesia without a single lung abscess.

Results of treatment will be considered in a later section, but it may be stated here that these are not so good as to suggest that the incidence in this series is seriously inaccurate and all the evidence available would seem to point to the fact that the incidence of post-tonsillectomy lung abscess in this country is very much less than it is in the United States. For purposes of comparison the results of the more important series of cases are summarized and contrasted in Table X. These observations, and the contrast between the incidence in the United States and in other countries, may

have a direct bearing on the elucidation of the cause of this variety of lung abscess.

TABLE X  
*Causes of Lung Abscess*

Year, author, and reference.	Operations on respiratory tract.			General operations.	Pulmonary inflammations.	Cause not evident (primary).
	Tonsils.	Teeth.	Other operations.			
1918 Lewis (212)	4	—	—	—	—	—
1919 Wessler (357)	21	—	1	5	37	21
1919 Hedblom (139)	6	6	—	—	12	—
1920 Lemon (206)	5	7	—	5	50	12
1921 Whittemore (362)	17	3	1	—	—	—
1922 Lockwood (218)	16	3	2	2	13	7
1923 Heuer and Mac-Cready (147)	4	—	—	12	31	—
1923 Homans (158)	7	3	—	3	5	3
1924 Lambert and Miller (202)	8	2	—	8	16	22
1925 Lord (223)	49	21	8	18	—	76
1925 Greer (124)	7	1	—	4	16	4
1927 Ballou (14)	8	11	1	7	26	8
1928 Kernan (180)	27	—	—	10	33	20
1929 Flick, Clerf, Funk, and Farrell (99)	97	—	10	14	43	3
1930 Pinchin and Morlock (278)	4	—	—	—	—	16
1931 Moersch (249)	31	5	5	5	29	24
1932 Frank (106)	7	—	—	11	15	12
1933 This series (single)	3	—	7	38	43	16
(multiple)	—	—	4	9	6	7
1924 Norris and Landis (267) multiple	—	—	—	7	9	2

Although the aspiratory theory was favoured by American writers at first, Fetterolf and Fox (93) considered that the condition results from sloughing of tissue directly on the pterygoid and pharyngeal muscles which, by their constant movement, dislodge small emboli which are arrested in the lungs. There is also the possibility that the negative pressure in the jugular veins assists in the displacement of septic material. C. and C. L. Jackson (170) have also studied the problem bronchoscopically and have reached the definite conclusion that this variety of lung abscess is embolic as a rule and is rarely, if ever, the result of aspiration.

In a symposium on this subject held in 1932, Bernard (205) sums up the argument against both the aspiratory and the embolic theories and considers that the infection reaches the lung by way of the lymphatics. Dunham (79) has shown that infection can pass freely into and through the interstitial tissue of the lung by way of the lymphatics and may thus give rise to pulmonary suppuration, yet the work on this subject is too scanty to permit conclusions to be drawn. The arguments in favour of the lymphatic theory derive such strength as they possess chiefly from the

obvious weaknesses of the rival theories which have previously attracted the main attention of observers. The possibility of this route of infection has also been shown by the work of Sabin (296), Clendening (59, 60), and other workers quoted by Schlueter and Weidlein (303).

Certain other clinical observations bearing upon the question of the causation of the post-tonsillectomy lung abscess may be considered at this stage. Myerson (260), in a series of direct observations, found that foreign material was evacuated from the bronchi in about twelve minutes, even under anaesthesia, and in the absence of the cough reflex. He later (261) examined bronchoscopically 100 cases in which tonsillectomy had been recently performed under light general anaesthesia and found that blood was present in the bronchi in 76 cases, in all of which the laryngeal reflex was present. Of 24 cases in which the bronchial tree was clear, 18 had coughed during the operation. The results indicated that the laryngeal reflex does not ensure the presence of cough when the pharyngeal contents come in contact with the larynx, trachea, or bronchi, and that only when there is increased irritability of the respiratory tract does the patient cough under light anaesthesia. Blood mixed with mucus and saliva does not produce a sufficient stimulus to activate the cough reflex, and cough is not the normal mechanism of expulsion under light anaesthesia. Similar results have been reported by Iglaue (163), who found that after tonsillectomy blood was present in the trachea in 40 per cent. of cases in which general anaesthesia was used, and in 38 per cent. of cases in which the operation was performed under local anaesthesia. He considered that post-tonsillectomy lung abscess may be explained as the result of prolonged retention of aspirated blood, crypt contents, and infected material in the bronchi. Ochsner and Nesbit (268) found that, after infiltrating the peritonsillar tissues with local anaesthetic, and placing lipiodol in the mouth, a large proportion of the lipiodol invariably entered the larynx and could be demonstrated radiographically in the bronchi. They, therefore, support the aspiratory theory.

Pancoast (271), from a radiological study, has reached the conclusion that the majority of post-tonsillectomy abscesses are embolic in origin, a view which is endorsed by Norris and Landis.

The subject will be considered further in the subsequent sections on general aetiological factors and on experimental work. It may be stated, however, that in one of the two cases in the present series in which lung abscess occurred after tonsillectomy, septic blood-clot was present in the jugular vein, and there was no doubt that the condition was embolic.

*Sinusitis.* In addition to tonsillectomy, lung abscess has at times been known to follow operations on the nasal sinuses, according to Yankauer (372), Wessler (357), Lynah (229), and Whittemore (362). Iglaue (163), Myerson (260), Ochsner and Nesbit (268), and Singer (311) have all emphasized the ease with which organisms may descend from the nose to the bronchi by way of the air passages. Yet sinusitis does not appear to be

a common cause of lung abscess. In one of the cases in this series, in which this complication occurred, there was local septic thrombosis and the abscess had undoubtedly resulted from septic embolism.

*Dental extraction.* The same difficulty is encountered in explaining lung abscess which follows the extraction of teeth, although the complication does not appear to be nearly so common as after tonsil operations. Cases have been described by Forbes (100), Lord (221), Ballou (14), and others.

*Foreign body.* Although it might be assumed that foreign body is a common cause of lung abscess, it does not appear on investigation to hold any important place in the published records. Cases have been recorded by Fenger (92), Clarke and Marine (57), Guisez (130), Guisez (129), Lynah (229), Yankauer (372), Morse (253), and Tucker (335).

Jackson (166) divides lung abscesses into two groups according to the presence or absence of a foreign body. He distinguishes them according to the results of bronchoscopic treatment, from which better results are obtained when foreign body is the cause of the abscess. In his series of more than 100 cases, it was found that very often the foreign body had remained in the bronchus for months or even years without its presence being suspected, and that in this group there was little or no associated pneumonitis. It was found that the progress of abscess due to foreign body is so benign and slow by contrast to that of the other types that Jackson suggested that there may be some physiological or structural barrier against the invasion of suppurative processes by the endobronchial route.

Graham (118) regards foreign body as the most important cause of lung abscess in children, and he also states that broncholiths are a more common cause of pulmonary suppuration than is generally supposed.

*Other inhaled material.* At times, inhaled stomach contents are found in the bronchi, usually in cases in which abdominal operations have been recently performed; this was only noted in one case in the present series.

Lung abscess following immersion in sea water, and presumably the result of inhalation, has been described by Bullowa (41), Lynah (229) and Wessler (357).

*Abdominal operations.* The occurrence of lung abscess after abdominal operations has been frequently reported, and an idea of the incidence of this complication may be gained by a study of Table X. Although the condition appears to be relatively common, comparatively little attention has been paid to the mechanism of causation. Mikulicz (243), in 1901, was the first to regard these cases as embolic in origin, a view more recently supported by Cutler and Hunt (69, 70), who have reviewed the literature thoroughly and conclude that septic embolism is the cause of post-operative pulmonary lesions, although the nature and extent of the damage is probably determined to some extent by the existence of previous pulmonary disease. They state that the incidence of this complication is high, even when local anaesthesia has been employed, and they lay stress on the fact

that the liability to embolism increases with the mobility of the part upon which the operation is performed. De Quervain (76) states that three-quarters of the deaths following gastric operations are due to pulmonary complications, and that in a great many of the cases the processes are really embolic in nature. Wharton and Pierson (359) have reviewed 1,600 gynaecological operations and found that, of the 25 which developed pulmonary complications, 11 were embolic, 10 definitely inflammatory and 4 were doubtful. Herb (143) reported two cases in a series of 12,045 operations.

A study of the cases in the present series shows that there is an intimate connexion between the occurrences of lung abscess and the presence of sepsis in the operative field, an observation which points to an embolic origin for the majority of cases at least. In a small proportion of cases, five in the present series, the condition results from direct spread of a subphrenic or hepatic abscess through the diaphragm into a lower lobe, usually on the right side.

*Pneumonia.* The older writers considered pneumonia to be a frequent cause of lung abscess. Laennec (199) regarded it as common, and saw 23 such cases in 1823. Zenker (380) reported pneumococcal lung abscess in 1892, and Tuffier (336) stated that in his series of 49 cases of lung abscess in which operations were performed, the cause of 23 could be traced to lobar pneumonia. Fraenkel (102), however, in a series of 1,200 cases of lobar pneumonia found evidence of lung abscess in less than 2 per cent. and Aufrecht (9) found only three lung abscesses in a series of 253 fatal cases of lobar pneumonia. Hamman (132) also quoted Aufrecht's series of 1,501 cases of lobar pneumonia, none of which developed lung abscess. Eisendrath (84), in 1901, collected reports of 25 post-pneumonic abscesses, of which 9 occurred in children under 12 years of age, and all of which recovered after drainage. McRae (233), in the following year, reviewed the literature and reported 73 of Eisendrath's cases, and 2 of his own, and Garré and Quincke (109) in 1903 thoroughly reviewed the literature for the previous twenty years and added a summary of 278 recorded cases. Pneumonia was held to account for 15 out of 20 cases described by Tilton (331) in 1907, and the operative mortality was 50 per cent. Von Eberts (349) regarded the majority of lung abscesses as being influenzal or pneumonic in origin, and Guinon (128), as has already been noted, first suggested the use of the term 'hepatisation grise suppurée' in 1912. Kuelbs (198), in the following year, described a series of 27 cases of abscess complicating acute respiratory infections, and Scudder (306), in 1914, described a further 7 cases.

A few years later, however, the part played by pneumonia in the causation of lung abscess assumed less importance, perhaps as the result of the increasing attention which was being paid to the effects of tonsil operations. Lockwood (218), in 1922, was only apparently able to find references to 127 cases reported as consequent upon lobar pneumonia, and Whittemore (362) stated that lobar pneumonia is seldom, if ever, a cause, although

he admitted that broncho-pneumonia and influenza play some part in the aetiology. Cecil (52) in 1929, reported 1,000 consecutive cases of lobar pneumonia, none of which developed lung abscess, and Keller (178) more recently still, has stated that while pneumonia was once thought to be a prime factor in the aetiology of the condition, it is now realized that most cases are post-operative.

The aetiological factors in the series of cases recorded here tend to show that pneumonia of either variety is a not unimportant cause of lung suppuration and that, when this complication occurs, a single abscess usually results. There is, therefore, support for the older view as to the relationship between the two conditions, and there cannot be any doubt that pneumonic lung tissue may at times break down and form an abscess cavity without the intervention of any further factor.

*Malignant growths.* In most published series, the cases which resulted from bronchial carcinoma have been omitted, but it is desirable to realize that a case which appears to be one of primary lung abscess may in reality harbour a carcinoma in the bronchus proximal to the suppurative lesion, in which case the prognosis and treatment are entirely altered. In a series of 184 cases reported by Maxwell (240) there were 38 cases of lung abscess and 15 of gangrene, a total incidence of 29 per cent. The coincidence of the conditions is, therefore, common, and although in many of these the presence of the growth is obvious clinically, yet the abscess is the more prominent feature in a sufficient proportion to make it essential for routine bronchoscopic examinations to be performed in all cases in which there is any possibility of the presence of a growth.

*Injury to the chest.* Lung abscess is an occasional complication of chest injuries, and cases have been described by Ballou (14) and by Lemon (206); it occurred in two cases in this series, in one of which there was a streptococcal septicaemia, and the organisms had apparently settled in a damaged area of the lung.

*Pyæmia and septicaemia.* It may be accepted that cases in which there is a focus of suppuration, such as an osteomyelitis or an infected uterus, and which develop a lung abscess, have done so as the result of a blood-stream infection. Reference to Table VII makes it clear that either single or multiple lesions may occur in the lungs as the result of a blood-stream infection, although multiple lesions are distinctly more common. Frost (107) traced this mode of origin in 47 out of 148 cases, and other observers have also recorded numerous cases, although as the primary or the blood-stream infection dominate the clinical picture, the secondary pulmonary lesion is often overlooked during life and these cases are consequently omitted from clinical series.

*Primary abscess.* The incidence of primary lung suppuration has been variously estimated. Kindberg (181) indeed considers that 50 per cent. of all cases are of this type although, as can be seen from Table X, most observers do not report so high a proportion. One point of special impor-

tance has been noted in this series, which may have some bearing on the cause of the condition, in that it shows that it is more likely to affect a damaged lung. Out of 16 cases of primary lung abscess, 5 had previously been known to suffer from pneumonia, and 2 others from 'pleurisy', and it seems reasonable to regard this high proportion of cases showing evidence of previous pulmonary inflammation as evidence that lung abscess is more likely to occur in an abnormal lung.

A general idea of the other causes of lung abscess is conveyed by the tables already referred to, and, as they are relatively less important than those reviewed here, they need not be further discussed. Reference may also be made here to further general considerations of this subject published by Whipple (361), Neuhof and Wessler (264), Alteri (3), and L. W. Frank (106).

#### *Review of Experimental Work*

A great many experimental observations have been made in the past few years, and these may be divided into three groups. Firstly, experiments designed to show the result of the aspiration of infected foreign matter; secondly, embolic experiments; and thirdly, attempts to define the significance of such extraneous factors as the influence of cough, and the depth of the respiratory movements.

*Studies on the effects of aspiration.* Many years ago St. Clair Thomson and Hewlett (330) estimated that 1,500 or more organisms are taken into the air passages each hour in London, and they claim that the ciliary action of the lining epithelium soon rids the inspired air of bacteria, so that none reach the lower regions of the respiratory tract. Stillman (319) repeatedly found Type IV Pneumococci in normal mouths, and these organisms have been isolated from the lung in cases of post-operative pneumonia by Whipple (360) and by Cleveland (62), who therefore favour the aspiratory theory. Stillman (320), however, sprayed mice with cultures of these organisms, and a study of the resultant lesions indicated that, even in so susceptible an animal as the mouse, other factors than the mere presence of pneumococci in the lung are necessary for infection to take place. In animal observations, Jones (175) regularly found organisms in the lungs of the guinea-pig, rabbit, and calf, but less commonly in the mouse and rat. He concluded that the flora in the lower part of the respiratory tract probably depends, to some extent, on the type of animal, organisms being found more commonly in herbivora than in carnivora. The effects of the intratracheal injection of pneumococci have been studied by Kline and Winternitz (188), who found that pneumonia could be produced provided that the organisms were introduced into the smaller bronchi, the result being made more certain by section of the vagi; and by Lamar and Meltzer (200), who found that the intratracheal insufflation of pneumococci and *B. Friedlander* produced lobar pneumonia consistently in dogs. Winternitz and Hirschfelder (369), using

rabbits previously rendered aplastic with benzol, found that the animals showed much less resistance to pulmonary infection, and died more readily than the controls, but the pneumonic lung did not break down to form an abscess.

Aschner (7) has reported that his attempts to reproduce suppurative lesions in dogs by intratracheal insufflation of blood, pus, and cultures of organisms obtained from cases of lung abscess were uniformly unsuccessful. and Tunnicliff (337, 338), Scarff (298), and Smith (316) were each unable to produce lung abscess by the intrabronchial introduction of spirochaetes alone. Scarff, however, succeeded in five out of eight attempts by causing frontal sinusitis and subsequently soaking a pledget of cotton wool in the resultant pus, which was then introduced into a secondary bronchus, and he concluded that although anaerobic organisms were usually present, spirochaetes were not essential to the process, and that a material factor in the production of the abscess was the obstruction to free bronchial drainage, which must be maintained for several days in order to ensure a successful result; his unsuccessful efforts included the introduction into the trachea of infected foreign bodies, simple destruction of lung tissue, the transpleural injection of organisms, and combinations of these methods. D. T. Smith (313, 314, 315, 316) produced lung abscess by injecting a mixture of *Sp. microdentium* vibrios, small fusiform bacilli, and anaerobic streptococci into the groins of guinea-pigs and by transferring the resultant necrotic material to the bronchi of other animals. He concluded that oral anaerobes were commonly but not invariably the cause of lung abscess. Smith's most recent results showed that lung abscess can be produced by aspiratory methods in 50 to 70 per cent. of cases.

Allen (2) produced lung abscess by first insufflating organisms and then by obstructing a bronchus, and Moise and Smith (250), in a study of spontaneous suppuration in the lungs of albino rats, reached the conclusion that atelectasis subsequent to bronchial obstruction is an important factor in the development of the condition; they point out that the literature contains numerous assertions that the lungs normally are sterile, and others to the effect that they frequently contain organisms without being obviously diseased.

Joannides (174) supports the aspiratory theory and summarizes the experimental work performed prior to 1928. In a series of careful but complicated experiments he succeeded in producing lung abscess by aspiration in twenty-one out of eighty-seven attempts. It is impossible to discuss his results in detail, but he concluded that the essential factors in the production of lung abscess are (1) the abolition of the cough reflex under general anaesthesia, (2) the presence of mucus or blood in the mouth during anaesthesia, (3) the presence of certain organisms in the mouth, notably the common oral saprophytes, (4) the presence of chronic infection in the mouth or nasal sinuses, (5) the physical state of the aspirated material, increased viscosity causing difficulty in expulsion, (6) functional deficiency of the cilia,

and (7) specific immunity of the lung to certain organisms, notably staphylococci. He also found that gastric contents introduced into the bronchi were capable of causing lung abscess.

Hedblom, Joannides, and Rosenthal (142) produced abscesses in twenty out of sixty-seven dogs by various aspiratory methods; their highest proportions of success followed the injection of spirochaetes from a lung abscess mixed with fresh dog's blood, which gave a positive result in ten out of fourteen cases. They pointed out that the cough reflex must be controlled in order to allow the infected material to settle in the alveoli. In one of their dogs, which developed an aspiratory abscess, a post-mortem examination seven days after the commencement of the experiment showed a typical abscess which was already completely shut off from the bronchus.

Kline (183) studied the influence of pulmonary trauma in determining the type of lesion produced by the aspiration of spirilla and fusiform bacilli in guinea-pigs and the nature of the lesions which followed tracheotomy in rabbits, and further studies have been reported by Veszprémi (347), Bethune (29), Harkavy (133), Mullin and Ryder (258), and by Zagarese (378), who stresses the factor of bronchial obstruction in the production of lung abscess.

The effect of posture on the aspiration of foreign material has been specially studied by Corper (67), who found that fluid placed in the nose of anaesthetized dogs and rabbits was easily aspirated when the animal was in the horizontal position, but this did not occur in the absence of anaesthesia. In the vertical position, however, rabbits were able to aspirate fluids into the lower lobes. It was found that carbon particles were heaped up at the bifurcations of the bronchi and did not reach the alveoli, whereas aspirated blood could be recognized in the alveoli of rabbits as long as four weeks after the intratracheal injection. Lemon (207) has also studied this aspect of the matter in dogs, and concludes that aspiration can occur whether the anaesthesia be light or deep, but that it does not occur except under anaesthesia; the position of the head above the body did not affect the result in his experiments, but when the head was lowered to a point 28.75 cm. below the feet, aspiration did not occur.

Cecil and Blake (53) performed aspiratory experiments on monkeys and found that inflammatory changes occurred in the lung parenchyma following the injection of cultures of virulent organisms several hours before exudate could be demonstrated in the air vesicles; they concluded that in cases of lung abscess pus can form in the lung before actual consolidation takes place. Lambert and Miller (202) performed similar experiments, also in monkeys, and carried out tonsillectomy in one animal, but were not successful in producing lung abscess.

*Studies on embolism.* Cutler and Schlueter (71) attempted to produce lung abscess in dogs by aspiratory methods and were uniformly unsuccessful. They then created an artificial embolus by excising a segment of a small vein, in which known organisms were placed, together with a small piece of

lead filing. The embolus so constructed was then introduced into the femoral or jugular veins of dogs, and a pulmonary abscess resulted in every instance, and this result was attributed to the localizing of the inflammatory process caused by the encapsulation of the infected material. It was found that 60 per cent. of the emboli lodged in the left lower lobe, presumably because of the straighter course of the left pulmonary artery in the dog. They concluded that the important factors in the production of lung abscess are the dislodgement of emboli from an infected site and the local immunity reactions of the lung, but the type of organism, the physical character of the embolus, and the number and virulence of the organisms, both pathogenic and saprophytic, already present in the air passages, were considered to be further factors concerned in the determination of the nature and extent of the lesion. Herrmann and Cutler (145) regularly obtained abscesses in animals by introducing emboli containing mouth bacteria; the anaerobes appeared to be the essential organisms. Weidlein and Herrmann (353) introduced septic emboli intravenously and produced lesions resembling lung abscesses which regularly healed spontaneously in three weeks. This work followed upon previous experiments by Schlueter and Weidlein (302), who also failed to produce chronic lesions by this method. Holloway, Schlueter, and Cutler (153) found that the older the thrombus from which the embolus arises, and therefore, presumably, the more attenuated the organisms which it contains, the greater the liability to a minor pulmonary lesion, whereas recent thrombi containing virulent organisms were found to give rise to diffuse suppurative or pneumonic lesions. They postulated that lung abscess lies midway between the two extremes, and considered the three main variable factors to be the virulence of the organisms, the character of the embolus, and the resistance of the patient. This latter factor is important in that good resistance exercises a localizing influence upon the lesion. Holman, Weidlein, and Schlueter (157) reported the successful production of embolic lesions in twelve out of seventeen attempts, although the results were not consistent.

The factors concerned were further discussed by Holman, Chandler, and Cooley (155), who concluded that the formation of an abscess depends, to some extent, on the occurrence of further thrombosis in the pulmonary arterioles, with consequent increase in the size of the infarcted area. Holman (154) obtained negative results from bronchial obstruction in dogs, whereas the introduction of infected emboli into the jugular vein was successful in fifteen out of twenty-one cases. The average incubation period was from six to nine days, which he compares with the incubation period of six days found in large series of cases which followed operations upon the upper respiratory tract, and he considered that the fact that the incubation period was the same, whether local or general anaesthesia was employed, is an additional argument in favour of the embolic theory. Moore (251), however, from precisely similar figures, drew the opposite deduction, and regarded an average incubation period of six days in his series as good evidence of

aspiration as opposed to embolism. Holman and Mathes (156), in a further study, compared the effects of different kinds of emboli in dogs anaesthetized with ether. They found that sterile emboli did not produce any recognizable lesion as a rule and suggested that, in all autopsies, the lungs should be inflated before being examined in order that the presence of sterile emboli should not be overlooked. They also noted that the bronchial artery is markedly dilated in the region of the embolus. Infected emboli produced either haemorrhagic infarct or abscess in twenty-eight out of thirty-two cases.

Lambert and Weekes (203) stated that the anaerobes found in many lung abscesses are pathogenic for dogs. They found that single, discrete abscesses can be caused by injecting an embolus composed of blood-clot containing a mixture of anaerobes, spirochaetes, fusiform bacilli, large Gram-positive bacilli, medium and small Gram-negative bacilli and Gram-positive cocci, but that pure cultures were not effective. In their cases, also, the average incubation period was six days. Hunter (160) found that a mixture of lipiodol, ground glass, and staphylococci injected intratracheally into rabbits was ineffective, whereas a similar mixture introduced into an ear vein produced a lung lesion in all cases, and in some a true lung abscess. Using an embolus composed of agar, which contained a known quantity of organisms, Tuttle (339) was able to produce a lung abscess with certainty in each of twenty-five dogs. Tuttle and Nicoll (340) have studied the effect of ligature of large branches of the pulmonary artery on the healing time of pyogenic abscess in dogs, and they report that this procedure appears to have no effect on the course of the disease if performed after encapsulation has begun; if performed early in the course of abscess formation, gangrene frequently results.

van Allen (342) and van Allen, Adams, and Hrdina (343) find defects in both explanations, and suggest, from experiments on dogs, that the correct explanation may lie in a coincidence of both factors. They conclude that the great vitality of the lung in pyogenic infections is due to its enormous blood-supply, and that elimination of the pulmonary circulation, such as occurs in embolism, reduces the blood-supply and thus lowers the vitality of the tissue, permitting the multiplication of organisms of low virulence already present in the deeper parts of the respiratory tract.

Certain other experimental evidence may be appropriately considered in this section.

The effect of cough upon the dissemination of foreign material inhaled into the respiratory passages has been considered by Archibald and Brown (4, 5), who studied cough to discover whether it had the effect of driving aspirated material further into the bronchioles. Using lipiodol and X-rays in lightly anaesthetized cats, they found that cough increased the rapidity and degree of penetration of the foreign material, but no similar effect of cough was noted when viscid sputum was substituted for lipiodol. They concluded that, although the usual action of cough is to expel material

from the bronchial tree, occasionally, and under favourable conditions, it may bring about the opposite effect. Ascoli and Boniades (8), working with rabbits, concluded that cough was a most important factor in keeping the respiratory passages clear.

The influence of anaesthesia, both from the point of view of aspiration, and on account of possible inflammatory complications of general anaesthesia alone, have attracted considerable attention. Hoelscher (152), as long ago as 1898, stated that during the course of every general anaesthetic, mouth contents find their way into the trachea and bronchi. Fairbrother and Hurst (87) have reported the spontaneous diseases which they observed in 600 monkeys, while investigating poliomyelitis. They noted that, in healthy animals, ether anaesthesia, even when prolonged or repeated at short intervals, was never followed by pulmonary complications.

Kelly (179) performed experiments on dogs which had previously been given charcoal by the mouth; a general anaesthetic was then given followed by apomorphine, and after the consequent vomiting the charcoal was always found to have entered the trachea despite the greatest care to prevent it by posture and swabbing the mouth and throat.

The lymphatic connexions of the lungs are beginning to claim increasing attention. Clendening (59) by injecting Indian ink into the tonsils has been able to demonstrate an intimate connexion between the lymphatics of the neck and those of the lung, but Harkavy (133) finds his evidence unconvincing.

#### *Résumé on Animal Experiments*

The experimental work already performed is comprehensive and the results obtained are conclusive, that in certain animals, lung suppurations can be caused artificially as a result of certain procedures designed to introduce infected material into the lungs either by way of the bronchi or by the blood-stream. Unfortunately, in a way, both sets of experiments have eventually been equally successful, and therefore they are not helpful in deciding the mechanism of causation of the disputed types of lung abscess in the human subject. Their validity as applied to the condition which occurs in man, is also open to question. With the exception of the experiments of Cecil and Blake (53) and Lambert and Miller (202) all of the significant work has been performed on quadruped animals, and it has been assumed that the results are equally applicable in bipeds. Yates (376), however, points out that in dogs, cats, and rabbits the pleura is thinner than in man, and states that the pulmonary circulation also differs in material respects in these animals. More important still is the consideration that in the animals commonly employed for experimental purposes the trachea is normally horizontal, as contrasted with the vertical position of the human trachea during the greater part of the day; Schlueter and Weidlein (302) in 1926 commented upon the difficulty which is experienced

in producing chronic lung abscess in dogs, and they considered that the horizontal position of the bronchial tree is responsible for the marked tendency to spontaneous healing.

It is not probable, and it is certainly not proved, that the mechanism which normally prevents particulate matter from entering the larynx in animals is exactly similar to that which functions in man, and it is quite unlikely that the methods by which the lower parts of the respiratory tract are kept free from invasion are precisely the same in the different species. In fact, common knowledge suggests that the cough reflex is a far more important safeguard in man than it is in animals, and it follows that it is unsafe to draw deductions from any of the aspiratory experiments performed on quadrupeds. The same objections do not apply with equal force to experiments on embolism, although no deductions may safely be drawn from the distribution of the lesions. The experimental work has clearly shown that pulmonary suppuration may be caused in animals by bronchogenic or by haematogenous infection, but consideration of a post-mortem series of cases leads to the same conclusion in man, and the result may be safely accepted. A study of the present series shows quite clearly that certain of the lung lesions resulted from embolism, while there is no reason to doubt that others, notably those which occurred after intracranial injuries or as a result of an oesophago-tracheal fistula, were the direct result of the aspiration of foreign material into the bronchi. It would seem that more light would be shed on the complex problem involved in this study if careful attention were paid to the clinical and pathological states found in the patient, and less to the results of artificial procedures in animals which may give rise to specious, and misleading conclusions. Logically, it is desirable that further animal experiments should be confined to the higher apes.

#### *Discussion on the Cause of Lung Abscess*

The greater part of the pathological investigations, animal experiments, and clinical speculations which have been devoted to this study have been directed to a single end, namely, to show that lung abscess results as a rule from one only of the two chief possible routes. Thus the exponents of each theory, as a result of their experiments, claim that the method in which they are primarily interested is the cause of the majority of the cases of post-tonsillectomy abscess, and they find grounds for the criticism of their opponents' experiments. So successful have both schools become in the experimental production of lung abscess, and so convincing are the arguments of the pathologists and clinicians, that the position is now peculiar in that it seems necessary to consider, not why post-tonsillectomy lung abscess is so common, but rather why it does not occur more frequently.

The position has been admirably summarized by Schlueter and Weidlein (303) who support the embolic theory in the case of post-operative abscesses.

They review the whole question from all points of view, and take into consideration the views of most previous writers. The exponents of the aspiratory theory base their opinion upon the fact that post-operative lung abscess usually occurs when general anaesthesia has been employed, and especially follows operations upon the upper respiratory tract. They also stress the frequency of involvement of the lower lobes, and finally the ease of experimental production of lung abscess by the aspiratory route. Against these conclusions, Schlueter and Weidlein point out the known occurrence of post-operative pulmonary embolism, and the tendency for lung abscess to occur when the operation is performed in a mobile field, especially if it be infected. The occurrence of post-operative lung abscess after local anaesthesia has been frequently reported, and the adoption of improved methods of general anaesthesia appears to have had little influence upon the incidence of the condition. The involvement of the lower lobes may equally be used as an argument by either side, as may be the other points brought forward by these writers, the incubation period and the sudden onset of symptoms. It is true that lung abscess is rare when a foreign body is lodged in a bronchus, and the significance of this may be admitted. The arguments of neither side are entirely convincing.

If the aspiratory theory be correct, then the observations of Myerson and Iglaue, that blood is present in the trachea immediately after operation in more than 50 per cent. of cases cannot easily be reconciled with Moore's incidence of one in 2,500 cases; on the other hand, if Fetterolf and Fox be correct, it is difficult to understand why embolism after the operation is so comparatively infrequent. The pathological fact that post-tonsillectomy abscess is nearly always single is also difficult to explain, for emboli are commonly, although by no means invariably, multiple, a point which is brought out in Table VII, and, while the cases in this series are far too few to yield any guidance, the larger series of cases of post-tonsillectomy abscesses do not contain any reference to multiple lesions. This alone would appear to be almost conclusive as showing that embolism is not the most important cause.

Approaching the problem from another aspect, it is remarkable that the incidence of the condition in the United States appears to be so much greater than it is in this country. There is no obvious technical reason why this should occur if the embolic theory be correct, for the chief difference is that in the United States the operation is usually performed with the patient sitting up, whereas in this country the patient is usually supine, and this suggests that aspiration plays some part in causation. There must, however, be some additional local factor in the lung, possibly a failure of the expulsion mechanism with retention of infected material in the bronchioles, or even an actual collapse of a small portion of the lung. It is also necessary to allow for the part played by variations in virulence of the organisms and the powers of resistance of the patient in each case.

It would appear to be true that lung abscess may arise either from

aspiration or from embolism, and that the part played by each of these may be important. The evidence suggests that the post-tonsillectomy abscess is more frequently aspiratory than embolic, and thus it is to be expected that measures taken to check the aspiration of infected material during the operation will materially reduce, although they will not entirely abolish the entire incidence of this condition.

With regard to the type of abscess which follows abdominal operations, the reverse holds good. It has been shown that some cases may result from a direct spread of infection through the diaphragm and that, in the majority of the others the operative field is infected. The aspiratory theory cannot explain why lung abscess should occur so much more commonly when there is local sepsis, whereas the embolic theory is most appropriate in this connexion. The main difficulty would appear to lie in the fact that most of the operations concern the portal venous system. In ten of these cases there were obvious abscesses in the liver, conclusive evidence of portal pyaemia and, when it is remembered that the liver rarely shows gross suppuration in cases of general pyaemia in which other organs are studded with abscesses, it is not difficult to imagine that organisms from the portal area could pass through the liver and thus reach the lung without leaving behind any macroscopic evidence of their passage. Reference to Table VII shows that, although this type is usually single, multiple abscesses are not uncommon. The evidence, therefore, suggests that, in this variety of abscess, the cause is more frequently embolism than aspiration.

The cause of the primary abscess is more difficult to determine, although the embolic theory is the more attractive in most cases. The existence of the group of cryptic multiple abscesses, which are clearly haematogenous in origin, suggests a blood-stream infection for single abscess at times. There appears to be some analogy between this group and bacterial endocarditis. In the latter condition the infecting organism travels by the blood-stream to a damaged heart valve, whereas the organisms present in the blood in septicaemia rarely cause similar lesions in the case of sound valves; so also, in some cases there would appear to have been previous lung damage which would encourage the deposition of organisms which might find themselves in the neighbourhood, for all bacteria which reach the blood-stream must inevitably pass through the lungs. On the other hand, it is possible that single lung abscess may result from a mild or abortive pneumonia and, in fact, it is often impossible to distinguish clinically between the two conditions at the onset. Pneumonia is seen, in Table VII, to be a frequent cause of lung abscess and the lesion is much more commonly single than multiple.

The purpose of this section is merely to summarize a large number of conflicting observations, and, by considering them in the light of the cases recorded here to attempt to assess the validity of the various views previously expressed. The fact which emerges is that lung abscess cannot be

considered always to be caused in one particular way, and that different types of abscess appear to vary somewhat in their mode of causation.

### *Treatment*

In view of the fact that the material of which this paper is composed is based entirely on post-mortem observations, it is useless to consider the details of the treatment adopted in these cases. Many lines of treatment have been advocated, and it would seem that the correct procedure in any given case must be determined by the position, size, duration, and cause of the abscess.

*Medical treatment.* The chief reason for the adoption of medical treatment, as opposed to more radical procedures, lies in the fact that there is a definite tendency to spontaneous recovery in a certain number of cases and that rest, posture, and drug treatment may materially assist this process. Yet the possibility of spontaneous recovery has been very variously estimated by different writers. Williams (368), from a study of a small series of cases, concluded that medical treatment is almost always fatal, and Picot (274, 275) also considered that preliminary medical treatment is unjustifiable, in that only 10 per cent. of his series of 133 cases were cured by medical means. Lenhartz (208) estimated the mortality to vary from 60 to 100 per cent., and similar views were expressed by Verneuil (346), Kissling (182), Baron (16), Mix (247), and Straub (322). Clarke and Marine (57) reported spontaneous recovery in only four out of their thirty-one cases, Whittemore (364) found that there were between 10 and 30 per cent. of cures following expectant treatment, and Lord (224) reported only 10 per cent. of recoveries as a result of medical measures. On the other hand, more promising results have been recorded by many observers. Tuffier (336) and Murphy (259) advocated a preliminary period of observation before considering surgical treatment, and Robinson (292) was strongly in favour of expectant treatment in cases where such a course is practicable. Isolated cases of spontaneous evacuation of lung abscess have been recorded by Bernard (24), Gounelle (117), Bertolini and Cerviño (27), Hutinel and Kourilsky (161), Kraus (196), Strauss (323), and by McKechnie (230), who discussed the influence of postural treatment in promoting spontaneous drainage and reported one case in which a lung abscess of five years' duration had been successfully treated by this method. In some series the results of expectant treatment were encouraging. Laennec (199) reported spontaneous recovery in eighteen out of twenty cases of post-pneumonic lung abscess, but in many of these the diagnosis is open to question. Wessler and Schwarz (358) estimated that one-third of post-operative lung abscesses in children cleared up spontaneously. Berry (26) reported 53 per cent. of cures by postural treatment, and Paillard (270) has commented upon the value of this method. In addition to the foregoing Mandelbaum (235) has reviewed the literature and has reported satisfactory results from the use of

a postural frame which he has devised in order to promote spontaneous drainage. The importance of postural treatment, both as a curative measure, and as a preliminary to operation has been emphasized by many writers, notably by Schaefer (299, 300), Lord (221), Carmody (49), Whittemore (363), Dorendorf (78), and Cherry (55).

There is little agreement as to the effect of treatment by drugs. Organic arsenical compounds have been regarded as almost specific by Maes (234), and good results have also been reported by Graham (118) and by Kline and Berger (187), whereas Weidlein and Herrmann (353) were not impressed by their results. Castex, Heidenreich, and Repetto (51) have introduced neoarsphenamine directly into the bronchi, and Mosny and St. Girons (255) have similarly employed electrargol with good results.

Success has been claimed as a result of treatment with emetine by Bernard (25) and by other writers, mostly of the French school. Quite recently very good results have been claimed as a result of intravenous injections of 33 per cent. solutions of alcohol by Fejgin (91) and Nandris (262), but the method does not appear to have been used in this country.

In considering the principles of treatment which should be adopted, it is impossible to give the views of each individual writer, but the subject has been fully considered on many previous occasions.

Lockwood (218) considered the position in 1922 and advised surgery only after an adequate trial of medical measures, and Spector (318) was strongly in favour of expectant treatment, for out of 19 cases 11 were stated to be cured and 6 others greatly improved by these means alone. Chandler (54) and Tudor Edwards (80) have discussed the subject from the medical and surgical points of view and agree that medical treatment is the method of choice in the earlier stages, and that this alone is frequently sufficient. Alexander and Buckingham (1) discussed the merits of the various lines of treatment very fully, and point out that the selection of the best therapeutic procedure for each type of case must be highly individualized. Dankser and Tchireikin (72) prefer conservative treatment as a routine. Muller (256, 257), Flick (98) and Georg (111) have reviewed the literature in some detail, and on the whole agree with the foregoing conclusions. Lambert and Miller (202) regard the treatment of acute abscess as primarily medical, and report 14 out of 30 cases cured by posture, whereas their results of drainage operations showed 11 cured out of 27 cases; only 1 out of the 30 medically-treated cases died, whereas 15 of the surgical cases terminated fatally. In a very complete survey of the subject, however, Morrison Davies (74) stated that the mortality of a large series of cases treated medically may be 55 to 70 per cent., or even more, whereas the operative mortality is about 30 per cent. He appears to favour surgical treatment, but agrees that cases of acute abscess should receive medical treatment for a period not exceeding two months. Smith (316) has also reviewed the literature very recently. By pooling the results of various observers, many of which have been quoted here, he collected a series of 1,018 cases, and of 607 treated medically, 157

(25 per cent.) recovered completely, and 249 (40 per cent.) died, while 333 cases were operated upon, of which 110 (33 per cent.) were cured and 133 (40 per cent.) died.

*Artificial pneumothorax.* This is the most debatable of all the procedures adopted in the treatment of lung abscess. Forlanini (101), the originator of pneumothorax therapy in pulmonary tuberculosis, is usually stated to have also been the first advocate, in 1910, of this line of treatment of lung abscess, yet Murphy (259), as long ago as 1898, advocated an open operation in order to allow the lung to collapse in cases in which the pleural cavity was free from adhesions, and he was thus, perhaps, the first to practise this line of treatment. Tewksbury (325, 326, 327, 328) has claimed excellent results from this method, including a series (327) of 14 cases, of which 11 recovered completely and 3 died. Other successful results have been reported by Busch (43), Bredow (36), Jacobaeus (171), Rich (286), Balboni (13), Izar (165), and Basabe (19). Greer (123) reported a case of apparent interlobar empyema draining into a bronchus which was successfully treated by this method.

In discussions on the subject Whittemore (364), Bergmann (23), Lilienthal (215), Eggers and Kernan (83), Hedblom (140) and Burrell (42) have all considered that collapse therapy has a place in the treatment of those cases in which the abscess is deeply seated and in communication with a bronchus.

Still more venturesome are those who employ pneumothorax as a diagnostic measure either in cases of suspected lung abscess or in order accurately to localize the lesion. Faulkner (89) considers it to be of great assistance and without risk, and Heuer and MacCready (147) and Singer and Graham (312) share this view.

There can be no doubt, however, that collapse therapy is often unsuccessful, and at times dangerous, as a result of infection of the pleura. Lambert and Miller (202) treated seven cases without improvement, and Lambert later considered the method too dangerous to be employed as a routine procedure. Piéry and Barbier (276) recorded a fatal case and emphasized the dangers of interference with the pleura, and in discussions the objections to collapse therapy have been held to outweigh its possible benefits by Young (377), Krampf (195), Smith (316), Brauer (35), Muller (256, 257), Wessler (357), and Chandler (54); Lockwood (218) and Whittemore and Balboni (365) have also reviewed the subject and are not enthusiastic advocates of this line of treatment.

A consideration of the reported results leads to the conclusion that the disadvantages and possible dangers of collapse therapy are such that it is not suitable for routine use. In occasional cases in which improvement is not taking place, where the abscess is deeply seated and in communication with a bronchus, it may perhaps be employed with benefit, but the risk attendant upon the induction of pneumothorax for diagnostic purposes would appear not to be justifiable. A reference to the state of the pleura

in the cases of the present series makes it clear that interference with the pleura is not likely to prove advantageous as a rule.

*Bronchoscopic treatment.* There appears to be considerable doubt as to the value of bronchoscopic procedures, although there can be no question of the necessity for an examination at the beginning of treatment in order to exclude the presence of a foreign body or a growth in a bronchus. Either of these conditions may be present without giving any distinctive signs of its presence. Recently Guisez (129) has described three cases in which a latent foreign body was detected by the bronchoscope, and Jackson (166) states that very often a foreign body may lie concealed in a bronchus for months or even years without its presence being suspected.

Reported results of treatment, either by suction or by washouts, carried out through a bronchoscope, vary considerably, although those most expert in the management of the instrument have apparently attained a considerable measure of success in suitable cases.

The uses of the bronchoscope in treatment were first pointed out by Yankauer (372, 373) in 1918, and he was followed by Lynah (227, 228, 229), who concluded that the earlier bronchoscopy is performed the more likely is the patient to recover, and that most of the cases in which recovery ensues are aspiratory in origin; he advocates bronchoscopic suction combined with a local instillation of bismuth or colloidal silver. Mayer (241) recorded a series of 9 cases in which promising results were obtained, but pointed out that treatment might need to be prolonged. Moore (252) discussed 38 cases of pulmonary suppuration treated bronchoscopically, and stated that the lesion is more frequently central than peripheral, a finding not in agreement with that of most observers, so that early bronchoscopy should be the logical means to facilitate drainage. In his first 13 cases one-quarter were cured and only one-third were not improved, results which approximate to those obtained by posture and medical means in other series. Moersch (248, 249) claimed excellent results, 16 out of 19 cases treated in 1925 and 1926 being cured, and he further reported 51 cures out of 105 cases in 1931. Similar good results were claimed by Kramer (194), Eggers (82), Tucker (335), and by Clerf (61), who reported 58 cases of lung abscess following tonsillectomy which were thus treated within three months of the onset, of which 46 recovered completely.

Jackson (166, 167, 168, 169, 170) has written extensively on the subject, and considers that the best results are obtained when a foreign body is present, although bronchoscopy has also the effect of preventing stagnation of pus, and therefore tends to promote healing.

In this country the literature of bronchoscopic treatment of pulmonary suppuration is scanty, but Pinchin and Morlock (279) state that by this means a high proportion of satisfactory results can be obtained in acute cases and excellent results in chronic cases.

In recent years the method has been successfully adopted in France, and Soulas (317) has reported good results. Bloch and Soulas (32) have recently

reviewed the subject, and conclude that, whereas the recovery rate without operation is about 20 per cent., this figure can be considerably increased by bronchoscopy, and they stress the necessity for early treatment in acute cases. They do not, however, support their contentions with figures.

Not all writers, however, are so enthusiastic as those already quoted. Kernan (180) considers the results of bronchoscopic treatment to be disappointing. Muller (256) is sceptical of its value without the assistance of other methods, and Miller (245), in a bronchoscopic study of 100 cases, is more critical of his results than the majority of bronchoscopists; he states that 59 of his cases were arrested or improved, and is careful not to claim actual cures as the result of treatment. Davies (74) is doubtful as to the value of bronchoscopy alone; Edwards (80) has also found that the results of endoscopic lavage do not fulfil his expectations, and Connors (66) states that bronchoscopy is not as a rule successful.

*Surgical treatment.* The pioneer work has already been considered in the historical review. Recently the trend of opinion has been in favour of conservative treatment when possible, and surgical treatment is being reserved for certain fairly well defined groups of cases.

In the field of experimental lung surgery the original work already referred to has been carried on by Green (122), who investigated the positive pressure methods of artificial respiration, and reported the results of transpleural operation in dogs, by Grégoire (125) on partial resection of the lung, and by Schlueter and Weidlein (302), who successfully performed lobectomy on dogs in which experimental lung abscess had been induced.

In 1908 Korte (192) reported a series of 37 cases of lung abscess and gangrene, of which 20 recovered and 9 died after operation, and in 1911 Upcott (341) advocated operation as early as one week after the development of symptoms as a routine procedure. Hitzrot (151), in 1915, reported a case in which lobectomy had been successfully performed for bronchiectasis and multiple abscesses, and about the same time Lilienthal (213) reported the results of drainage operations in 11 cases, of which 4 recovered completely and 4 died. Hedblom (139) stated, in 1919, that the mortality of the condition is strikingly reduced by early operation, and quotes Schulz (305) and others in support of this view. In this connexion it may be mentioned that Hedblom advocates exploratory puncture of the chest with a needle in order to localize the lesion, and in this he is supported by Lehmann (204), although Lockwood (218) and the majority of other writers are strongly opposed to this practice on account of the risk involved. In a later paper Hedblom (140) was in favour of expectant treatment, and advised drainage operations if the patient were not improving or if the condition had become localized and chronic. An exhaustive review of the surgical literature was given in 1922 by Aschner (7), and the subject is also considered in detail in Lockwood's (218) paper. Lilienthal (213, 214, 215, 216, 217) has published a series of papers in which he deals fully with the subject; he advocates that radical operation should be postponed for several months unless the

disease is spreading, but that interstitial abscesses should be drained before they open into a bronchus, and that all progressive lesions should be drained even in the early stages of the disease. Flick (98) and Lord (224) discuss the results of surgical treatment in detail, and find that the outlook is better in acute cases, but Miller and Lambert (246) point out that the mortality following surgical treatment depends, to a large extent, upon the skill and experience of the surgeon; they found that the operative mortality in acute cases was 65 per cent. (202) and were in favour of expectant treatment in this type. Graham (118, 119, 120) finds that he is operating on a smaller proportion of these cases every year, and considers that surgery is indicated only when the abscess is superficial; he prefers the operation of cauterly pneumectomy, and has reported 31 out of 45 cases to be free from symptoms as a result of this procedure. The operation of cauterly lobectomy has also been successful in the hands of Hedblom (140) in chronic cases in which there was associated fibrosis and bronchiectasis; Edwards (80), however, considers that lobectomy is never required for cases of single abscess. Harrington (135) found that in most cases several operations were necessary, and in his series of 111 cases there was an operative mortality of 9 per cent. and cure or relief of symptoms in 66 per cent. Davies (74) prefers operation after two months' medical treatment, and states that the average surgical mortality is 30 per cent. He advocates that all except the deeply-seated abscesses should be drained, and has obtained some good results from thoracoplasty in cases of chronic abscess with bronchiectasis in the upper lobe. Sauerbruch (297) performs a local operation in which the affected area is collapsed by the insertion of paraffin or muscle tissue, and Alexander and Buckingham (1) have also approved this procedure.

Extrapleural thoracoplasty is an operation which has resulted in many disasters in this type of case, and it has all the disadvantages of the artificial pneumothorax in addition to the mutilation attendant upon it, as well as as the finality of the procedure. The position has been summarized by Smith (316), who agrees with the great majority of surgeons that this operation is not suitable in the treatment of lung abscess.

Further reports and discussions have been published by Elkin (85), Sergeant, Baumgartner and Kourilsky (309) and by Brauer (35).

Phrenic evulsion is an operation which appears to have little direct influence upon the course of the disease, although it may be of some value as an adjuvant to thoracoplasty. Falta (88) obtained improvement in four cases as a result of phrenic paralysis alone.

#### *Summary of Treatment*

In spite of the variations in detail of the treatment advised by different writers, consideration of all the views expressed shows that there is a broad general scheme upon which these cases may best be treated, and at the same time it is generally agreed that the best results are obtained from an

application of the general rules to the circumstances of each individual case. The factors upon which the selection of the line of treatment depends are found to be: (i) The cause of the abscess. (ii) The duration of the abscess. (iii) The general condition of the patient. (iv) The nature and virulence of the infecting organisms. (v) The site and extent of the lesion. (vi) The presence of complications in the lung and pleura.

Unless the patient is obviously losing ground, it is now generally agreed that acute cases are best treated by non-operative means. Rest and postural drainage are the most important measures and should be adopted in all cases, while these may be supplemented by drug treatment, either organic arsenical compounds in cases in which spirilla appear to be the important infecting organism, or by non-specific medication. The use of the bronchoscope must remain optional as a method of treatment in the early stages, except in such as routine bronchoscopy reveals a treatable cause in the bronchus. Intrabronchial medication does not appear to be of great value. Operation should be reserved for such cases as are definitely becoming worse; failure to improve in the early stages is not necessarily an indication for surgical drainage.

If the condition should be stationary after efficient treatment for a period of at least two months, then further measures must be considered.

Bronchoscopic treatment may be expected to be beneficial in the case of hilar and central lesions, but it is not likely to cause much change in cases where the abscess is draining freely into a bronchus; the results of bronchoscopy are unlikely to be superior to those of efficient postural treatment.

Artificial pneumothorax should only be employed when the lesion is central or hilar in type, never when it is situated near the pleura. The abscess should be in free communication with a bronchus, and healing is obtained as a result of apposition of the walls and consequent obliteration of the cavity by fibrosis. In chronic cases, in which the granulation tissue lining the cavity has been replaced by a layer of epithelium, healing is unlikely to occur. This method of treatment is only suitable for the expert.

Surgical treatment is chiefly indicated when the abscess is peripheral, and when bronchial drainage cannot be established. In many of these cases the lesion is multilocular and, in such, satisfactory bronchial drainage of the condition is impossible to achieve. The best results appear to be obtained from the simplest procedures. A two-stage drainage operation is probably the safest of all the surgical methods and is, therefore, most suitable for routine use. Pneumectomy and lobectomy are very rarely necessary and are operations which should not be lightly undertaken. Thoracoplasty may be expected to relieve symptoms in a small proportion of the very chronic cases, but the results of this operation have not justified the expectations of those who first advocated its use in this condition.

Finally, it must be realized that preventive measures designed so far as possible to avoid the occurrence of this condition as a complication of operations in general deserve further study, for, if the post-operative group of cases could be abolished, lung abscess would become much less common and these intricate therapeutic problems would arise less frequently than is the case at present.

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## THE EFFECT OF YEAST AND WHEAT EMBRYO IN ANAEMIAS:

### II. THE NATURE OF THE HAEMOPOIETIC FACTOR IN YEAST EFFECTIVE IN PERNICIOUS ANAEMIA<sup>1</sup>

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IN a previous communication (28) it was noted that certain commercial preparations of yeast and wheat germ could influence blood regeneration in pernicious anaemia. It was suggested that yeast extracts might owe their potency to one or more of the following factors: (i) extrinsic factor; (ii) a breakdown product of the extrinsic factor, perhaps resulting from the interaction of this substance with an enzyme liberated during the autolysis of yeast; (iii) small quantities of a substance resembling the 'liver active principle'.

These possibilities have been investigated as follows:

(i) In order to avoid contact with traces of intrinsic factor possibly present in the gastric juice of cases of Addisonian pernicious anaemia, yeast products which influenced blood regeneration when given orally have been administered by other routes.

(ii) Experiments have been made to determine whether or not material potent for pernicious anaemia may arise or increase during the autolysis of yeast.

(iii) To determine the presence or absence of a substance resembling liver active principle, the methods used for liver extract (4) (17) have been applied to yeast. These and other yeast fractions have been administered parenterally to avoid contact with the patients' gastric juice.

By extracting the yeast in various ways, an effort has been made to obtain the haemopoietic material in a more purified form. A possible relationship between haemopoietic activity and the vitamin B complex has been investigated.

#### *Methods*

The clinical and haematological methods have already been detailed (28), and it is necessary merely to describe the preparation of the yeast fractions employed.

<sup>1</sup> Received March 24, 1934.

A. *Fractionation.* 1. *65 per cent. alcohol-soluble fraction of marmite (A.E.M.).*

(a) The method of preparation of this extract has been described (28). In a recent batch the pH of the yeast-alcohol-water mixture was about 4.4. The alcohol precipitate, which is rejected, contains most of the protein and salt, and a comparison with the original unflavoured marmite showed:

	Mineral matter (ash).	Nitrogen.
Marmite	13.4 %	7.92 %
Extract	1.23 %	0.436 %

Filtration of the marmite-water-alcohol mixture frequently took several days. To simplify this process the mixture was poured into a nainsook bag and the paste allowed to macerate in contact with the liquid which percolated through. The period of filtration was shortened, but the result was an extract much paler in colour than usual, and after it had proved ineffective in one case the modification was abandoned.

(b) *Autoclaved marmite.* In order to determine whether or not the active principle was heat-stable, marmite was autoclaved at 15 lb. pressure for five hours and subsequently subjected to 65 per cent. alcoholic extraction by the usual method. It was found necessary to dilute the marmite before autoclaving.

2. *65 per cent. alcohol-soluble fraction of fresh brewer's yeast (A.E.Y.).*

Because of the satisfactory results obtained with a 65 per cent. alcoholic extract of marmite, the same method of fractionation was applied to fresh brewer's yeast.

In the case of batch 1 the following method was used. 10 lb. (4.53 kg.) of pressed yeast were made into a paste with about 1.8 litres of water, and to this paste was added 3.6 litres of absolute alcohol. The whole was allowed to stand until the following morning, when the supernatant fluid was decanted through a moist filter, the remainder of the mixture being brought on to the filter in due course. Filtration was difficult, taking about three days, and was not materially facilitated by reduction of pressure. The filtrate was evaporated on a water bath, keeping the temperature below 90° C. In later batches the alcohol was evaporated under reduced pressure, the temperature being kept between 40° and 45° C. The residue was made up with distilled water so that 100 c.c. contained extract from 480 grm. of yeast.

A comparison with the original yeast showed:

	Mineral salts (ash).	Nitrogen.
Pressed yeast	0.275 %	1.12 %
Extract	1.33 %	0.53 %

The pressed yeast used in making these extracts was found to contain approximately 78.0 per cent. moisture. The pH of the yeast-alcohol-water mixture in successive batches was 5.5, 5.65, 3.5, 6.05, and 5.0.

In later batches the reaction was adjusted to the region of the isoelectric point, which was between pH 5.0 and 6.0. Portions of batches 5 and 10 were filtered sterile and found to be suitable for intramuscular use. Injection into rats did not cause toxic effect, nor was there local oedema or necrosis. In order to ascertain whether the yeast used for the preparation of these extracts was in a living state, specimens were stained with methylene blue by the method of Fraser (10). Living cells are not stained after several minutes, but dead cells are stained in one minute. Examination showed that the original yeast was composed almost entirely of live cells,

while on treatment with 65 per cent. alcohol nearly all the yeast cells were killed.

3. *Complete alcoholic precipitation of the 65 per cent. alcohol-soluble fraction of fresh yeast.*

By treating the 65 per cent. alcoholic extract to complete precipitation with alcohol, it was hoped to obtain a potent fraction of smaller bulk. 9.18 kg. of fresh pressed brewer's yeast were made into a stiff paste with 1.8 litres of water. 3.6 litres of absolute alcohol were added, forming a thin paste. The pH was adjusted to the region of the isoelectric point (about 5.5), and the mixture was allowed to stand overnight before being filtered. The filtrate amounted to 6 litres, and the residue on the filter paper weighed 5.37 kg.

The filtrate was concentrated at 37° to 42° C. under reduced pressure to 250 c.c. The concentrated liquid contained glycogen and nucleic acid, but much less protein than the original yeast. The isoelectric point of this liquid with alcohol was found to be in the region of pH 6.4. After adjusting the hydrogen ion concentration to approximately this figure, precipitation was carried out by running the liquid into sufficient alcohol to render it over 90 per cent. with respect to alcohol. The precipitate, a brown slimy mass, was dissolved in water, leaving a white insoluble residue weighing 3 gm., which, on analysis, proved to be calcium and magnesium phosphates, calcium sulphate, and a small amount of nucleic acid.

The volume of the filtrate containing the water-soluble fraction was such that 46 c.c. contained extract from 480 gm. of fresh yeast. In later batches the volume was less, and was adjusted so that 15 c.c. contained extract from 480 gm.

4. *Fractions obtained by lead acetate precipitation.*

During the process of precipitation with basic lead acetate the 'liver active principle' remains in the filtrate (4). An attempt was made to determine whether haemopoietic material in yeast would behave in a similar manner.

The yeast-alcohol-water mixture (batch 11) equivalent to 20 lb. of yeast prepared as above (2) was concentrated to approximately 250 c.c. *in vacuo* (temperature not exceeding 35° C.), and run into 3 litres of absolute alcohol with stirring. The resulting white precipitate was separated, washed with alcohol, drained, and dissolved in water. A part weighing 13.45 gm. proved insoluble in water, and was separated and dried *in vacuo*.

The aqueous solution (approximately 2 litres) was adjusted to pH 8 to 9 with ammonium hydroxide and precipitated at a maximum by lead acetate. The precipitate was separated and the two fractions freed from lead by  $\text{H}_2\text{SO}_4$  and  $\text{H}_2\text{S}$ . The resulting solutions were concentrated *in vacuo* to a volume of 300-400 c.c. and then heated rapidly to 75° C. 0.3 per cent. tricresol was added, the solutions were cooled to room temperature, and the reactions adjusted to pH 7 to 7.4. The solutions were kept at 5° C. for several days, filtered, and a part of each ampouled under sterile conditions.

Two products were obtained. Extract 'A', which contained the fraction not precipitated by lead acetate, amounted to 450 c.c., of which 1 c.c. was equivalent to 20 gm. of yeast. Extract 'B', which contained the fraction precipitated by lead acetate, amounted to 337 c.c., of which 1 c.c. was derived from 30 gm. of yeast. The solutions were injected intramuscularly into rabbits and found to give no local reaction or necrosis.

5. *The Medical Research Council process for liver extract.*

In an endeavour to determine the presence or absence of a substance resembling the 'liver active principle', yeast was subjected to the Medical Research Council process for liver extract (17). 10 lb. (4.53 kg.) of pressed brewer's yeast yielded 65.8 gm. of a yellow powder. Half of this quantity was made into a sterile solution of the Castle type (24), and put up in vials suitable for intramuscular injection (5 c.c. being derived from 100 gm. of yeast). A second batch of 10 lb. (4.53 kg.) of yeast yielded only 37.2 gm., of which half was rendered unsuitable for intramuscular injection (5 c.c. being derived from 100 gm. of yeast). In addition to undergoing the usual sterility tests, the intramuscular preparations were injected into rats in doses of 0.25 c.c. per 100 gm. body-weight. No toxic symptoms were observed, nor any necrosis or oedema at the site of injection. A third, much larger, batch (112 lb., 50.74 kg.) of brewer's yeast yielded powder at the rate of 127 gm. from 10 lb. of yeast.

B. *Methods of autolysis.* An effort has been made to determine the effect of autolysis upon the haemopoietic potency of yeast. Various methods of autolysis have been used.

1. *Ordinary autolysis.*

(a) 10 lb. (4.53 kg.) of yeast from the same batch as A.E.Y. (1) was pressed down in a glass vessel and covered with a layer of toluene to inhibit bacteria. The whole was kept between 23° and 25° C., and autolysis was allowed to proceed for eight-and-a-half weeks. At the end of this period the liquid and solid debris were well shaken together, and subjected to alcoholic extraction. The whole being in a fluid condition, the requisite amount of alcohol was added to render the concentration 65 per cent. with respect to alcohol. The method of extraction was otherwise similar to that used for the fresh yeast. The final product was adjusted so that 180 c.c. contained extract from 480 gm. of autolysed yeast.

(b) 10 lb. (4.53 kg.) from a second batch of yeast was allowed to autolyse in a similar manner. Autolysis proceeded fairly rapidly, and at the end of three weeks about a quarter of the total bulk consisted of a brown liquid. The 65 per cent. alcohol-soluble fraction was obtained as before.

2. *Acid autolysis.*

A portion of the batch of yeast used for extract A.E.Y. (5) was subjected to the process described by Herron and McEllroy (12), which was said to have greatly increased the potency of liver for blood regeneration in pernicious anaemia.

The yeast (5 lb., 2.26 kg.) was made into a paste with one-fiftieth normal hydrochloric acid, which was added to a total volume of 11½ litres. 50 c.c. of chloroform were added, the whole being well shaken and kept in an incubator at 37° C. for 10 days. The mixture was well shaken each morning, and at the end of the period the yellow liquid was filtered. The volume was such that 1.8 litres contained the equivalent of 480 gm. of yeast.

3. *'Extra-autolysed' marmite.*

The marmite was permitted to autolyse at the usual autolysing temperature for more than double the time usually allowed for this part of the process. The method was suggested by Wills and based on her observations (35) on the efficacy of marmite which had been heated in an autoclave. This marmite was supplied by the manufacturers, together with an equal quantity of control material.

*C. Vitamin B<sub>2</sub> concentrates.* These concentrates were used in investigating a possible relationship between haemopoietic activity and the vitamin B complex.

*Concentrate I* was prepared from an aqueous extract of baker's yeast by precipitation with neutral lead acetate. The precipitate was decomposed and treated with mercuric sulphate. The resulting mercury precipitate was then decomposed and kept somewhat acid ( $\text{H}_2\text{SO}_4$ ) to prevent deterioration. The total volume was 30 c.c., derived from 300 gm. of yeast.

*Concentrate II.* An aqueous extract of baker's yeast was treated with neutral lead acetate. The resulting precipitate was decomposed and made up into a solution which had a pH of about 3.0, and which contained a moderate amount of sulphate. The total volume was 500 c.c., derived from about 2,500 gm. of yeast. It was found that 0.5 to 1.0 c.c. daily was sufficient to supply the vitamin B<sub>2</sub> requirements of the rat.

### Case Reports

The various yeast fractions described above were administered orally, rectally, or by intramuscular injection in thirteen cases of pernicious anaemia. These cases form a continuation of the series previously reported (28), and for ease of reference they are numbered accordingly. Cases 19 and 20, which were briefly mentioned in the first paper, are here described more fully. The haematological tables have been abbreviated. Reticulocyte counts, although carried out daily, are given for alternate days only up to the peak of the response (if any), and for less frequent intervals afterwards and during the control period. In cases where charts are included, the tables have been further cut down.

*Case 19. Negative result from alcoholic extract of marmite per rectum, followed by a haemopoietic response to smaller doses by mouth.* H. D., female, aged 52, suffered from pernicious anaemia of six weeks' duration. Vomiting had occurred frequently during the previous two weeks, and the tongue had been sore for several days. Her husband had died three years previously at the age of 53 from pernicious anaemia. While he was alive she used to eat liver daily, but since his death had taken only a quarter of a pound a week. Fresh meat was consumed daily, together with adequate amounts of green vegetables and fruit. There were no neurological symptoms or signs. Gastric analysis after the subcutaneous injection of  $\frac{1}{2}$  mg. of histamine showed complete achlorhydria, with an absence of pepsin by Fuld's method.

At the commencement of treatment red-blood cells numbered 1.72 millions per c.mm., with 49 per cent. haemoglobin, giving a colour index of 1.2. White-blood cells numbered 5,000 per c.mm. Reticulocytes were 3.0 per cent.

Extract derived from 8 oz. (240 gm.) of marmite was given each day in divided doses per rectum. On the third day repeated vomiting occurred, and on the fourth day she looked dehydrated and ill, so that after extract from 2 oz. had been injected treatment was discontinued until the seventh day, when extract from 4 oz. was given without ill effect. Full doses were administered on the eighth, ninth, and tenth days. In all, extract from

54 oz. of marmite was given during a period of ten days, so that the average day dose was 5.4 oz. (162 grm.). As can be seen from the table, the result was negative.

The subsequent daily administration of extract from 4 oz. of marmite for thirty-one days produced the haemopoietic response shown in the table. Subjective improvement and increased appetite occurred, and there was an increase of 6 lb. in weight. There was no recurrence of vomiting or soreness of the tongue. The bowels remained regular. The temperature, which had shown irregular rises to 99° or 100° F., remained normal after the tenth day of administration of extract of marmite by mouth.

For ten days after discharge from hospital the patient took 4 oz. of marmite itself daily without much difficulty. The conditions with regard to absence of liver or meat from the diet were maintained during this period. At the end of this time the red-blood cells had increased to 3.58 millions per c.mm., with 90 per cent. haemoglobin. Although there had been no return of sore tongue or digestive symptoms, there had not been that dramatic increase in strength and in well-being usually associated with a liver-induced remission.

Treatment with marmite was therefore discontinued and replaced by equal amounts of cooked liver (120 grm. daily). After twenty-two days red-blood cells numbered 4.40 millions per c.mm., with 97 per cent. haemoglobin.

Days of observation.	R.B.C. $\times 10^6$ .	Hb. %.	Reticulocytes %.	Treatment.
1	2.01	51	1.2	None.
5	—	—	0.8	"
6	1.72	49	3.0	Alcoholic extract from marmite 240 grm. per rectum.
7 to 16	—	—	No rise *	" " "
17	1.65	46	3.6	Alcoholic extract from marmite 120 grm. by mouth.
18	—	—	2.8	" " "
20	—	—	4.4	" " "
22	—	—	6.2	" " "
24	—	—	7.2	" " "
25	—	—	8.8	" " "
26	2.05	54	8.6	" " "
33	2.39	62	4.8	" " "
40	2.45	64	1.2	" " "
46	3.04	75	1.4	" " "
48	2.86	71	—	Marmite 120 grm.
58	3.58	90	0.2	Liver 120 grm.
80	4.40	97	—	"

\* Reticulocytes at 8, 10, 12, 14, and 16 days were 2.8, 2.2, 1.0, 2.6, and 3.6 %.

*Case 20. Slight reticulocyte responses with vitamin B<sub>2</sub> concentrates followed by a good haemopoietic response to alcoholic extract of marmite.* H. S., male, aged 59, suffered from pernicious anaemia of six months' duration. There were no symptoms or signs of subacute degeneration of the cord. The diet was deficient in meat, which he disliked. He had two attacks of rheumatic fever in adolescence, and mitral stenosis was present, but the heart was only slightly enlarged, and there was no evidence of decompensation. Gastric analysis showed complete achlorhydria and only a trace of pepsin (less than two by Fuld's method) even after the injection of 1 mg. of histamine.

At the commencement of treatment (19th Jan., 1933) red-blood cells

numbered 1.38 millions per c.mm. with 36 per cent. haemoglobin, the colour index being 1.30. Reticulocytes 0.6 per cent. White-blood cells, 3,400.

The total available quantity of vitamin B<sub>2</sub> concentrate (No. I) was 30 c.c., derived from 300 gm. of baker's yeast, and this amount was given in divided doses over a period of seven days.

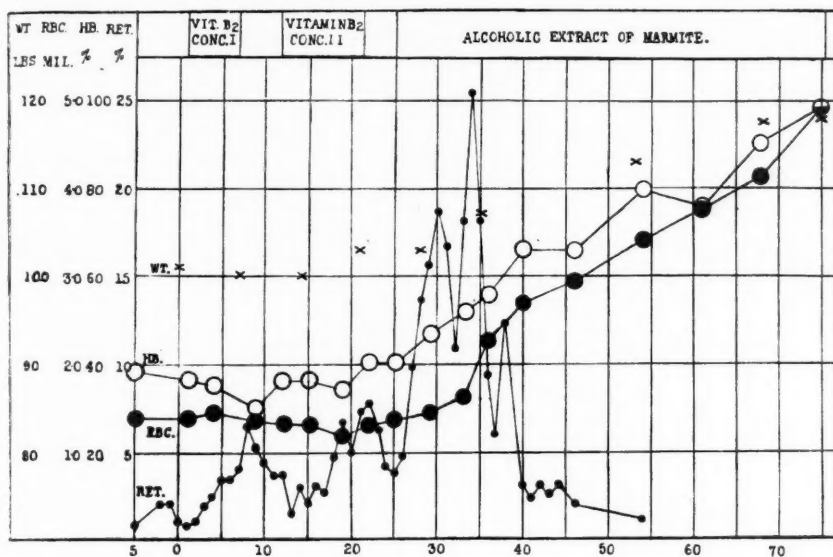


FIG. 1.

Days of observation.	R.B.C. $\times 10^6$ .	Hb. %.	Reticulocytes %.	Treatment.
1	1.36	38	0.8	None.
7	1.38	36	0.6	Vitamin B <sub>2</sub> concentrate I.
14	—	—	6.4	" "
18	1.30	36	3.6	Vitamin B <sub>2</sub> concentrate II.
28	1.28	40	7.6	" "
32	1.34	40	3.7	Alcoholic extract from marmite 120 gm.
40	1.62	47	18.2	" " "
41	—	—	27.2	" " "
43	2.26	56	9.4	" " "
53	2.93	66	2.0	Alcoholic extract unflavoured marmite 120 gm.
61	3.39	80	1.0	" " "
75	4.07	90	—	" " "
82	4.89	98	—	" " "
89	5.12	97	—	" " "

Vitamin B<sub>2</sub> concentrate (No. II) was available in large quantities, and the patient received daily for ten days 50 c.c., derived from 250 gm. of baker's yeast.

Apart from a small fluctuation of reticulocytes there was no significant haemopoietic effect from either of these concentrates, whereas the subsequent administration of an alcoholic extract derived from 120 gm. of marmite was followed by a marked response (Fig. 1).

This patient subsequently took half a pound (240 gm.) of cooked liver on six or seven days a week. On 9th March, 1934, about fourteen months after

the commencement of treatment red-blood cells numbered 5.78 millions per c.mm., with 110 per cent. haemoglobin. On further gastric analysis only very small volumes of juice were obtained, and there was no free hydrochloric acid even after histamine stimulation and the ingestion of 150 c.c. of 10 per cent. alcohol.

*Case 21. Mildly positive result from alcoholic extract of marmite in a case of pernicious anaemia with osteoporosis.* E. M., female, aged 54, suffered from osteoporosis and brittle bones combined with a clinical picture resembling pernicious anaemia. In the past year she had become completely crippled by a series of spontaneous fractures of the long bones, due to extreme osteoporosis. Examination of the urine, blood calcium, blood urea, and analysis of the faecal fat showed no very significant deviation from normal, and a diagnosis of adult coeliac disease could not be substantiated. The tongue, which was almost completely smooth, had been sore on and off for about eighteen months. The nails were brittle and longitudinally striated. The spleen was not palpable. There were no signs or symptoms of postero-lateral involvement of the spinal cord. The diet had included adequate amounts of meat and green vegetables, and there was no vomiting or diarrhoea. Gastric analysis, even after histamine stimulation, showed an absence of free hydrochloric acid and only a trace of pepsin (less than 4 units by Fuld's method). Red-blood cells numbered 1.40 millions per cmm., with haemoglobin 33 per cent., giving a colour index of 1.2. White-blood cells numbered 4,600. Platelets were diminished. The erythrocytes showed marked anisocytosis and megalocytosis, and some poikilocytosis; also a few microcytes with pale centres.

The administration of a 65 per cent. alcoholic extract from marmite, 120 grm. daily, was followed by a rise of reticulocytes which began on the sixth day, remained in the region of 10 per cent. from the eighth to eleventh days, and fell to normal on the fourteenth day. During the first eleven days the red-blood cells increased to 2.01 millions per c.mm. and the haemoglobin to 46 per cent. A fresh batch of extract used during the next two weeks was without effect upon blood regeneration.

The patient left hospital suddenly, and it was not possible to follow the effect of liver therapy. After discharge she took dried stomach in doses of two heaped teaspoonfuls daily, and in sixteen days the red-blood cells had only increased to 2.92 millions per c.mm. and the haemoglobin to 52 per cent.

Days of observation.	R.B.C. $\times 10^6$ .	Hb. %.	Reticulocytes %.	Treatment.
1	1.40	33	1.6	None.
3	—	—	1.4	"
6	1.36	33	1.8	Alcoholic extract from marmite 120 grm.
8	1.32	32	0.6	" " "
10	—	—	2.0	" " "
12	1.70	36	7.6	" " "
13	—	—	10.9	" " "
14	—	—	10.2	" " "
16	2.01	46	10.6	" " "
18	—	—	3.6	" " "
20	2.08	47	1.4	" " "
25	2.1	49	1.8	" " "
33	2.06	49	—	'Ecstomak' two heaped teaspoonfuls.
48	2.92	52	—	" " "

Case 22. (i) *Slight response to yeast extract (M.R.C. process) by mouth, followed by a negative result from the same extract given intramuscularly.* (ii) *Negative result with alcoholic extract of marmite (nainsook method).* C. L., female, aged 53, suffered from pernicious anaemia of two years' duration. There were no signs of postero-lateral degeneration of the spinal cord. Gastric analysis showed a histamine-refractory achlorhydria, and an absence of pepsin. At the commencement of treatment the red-blood cells numbered 1.38 millions per c.mm., with 42 per cent. haemoglobin, the colour index being 1.45.

The Medical Research Council process for liver extract, when applied to yeast, yielded a yellow powder, which was administered orally for ten days in doses derived from 480 gm. of yeast. The reticulocytes rose slightly to only 7 per cent. on the sixth day, and there was a small increase in red-blood cells and haemoglobin. When, after suitable manipulation, the extract was administered intramuscularly in amounts derived from 100 gm. of yeast daily the result was negative.

A 65 per cent alcoholic extract of marmite prepared by a modified (nainsook) method was then administered for ten days in doses derived from 120 gm. There was no significant fluctuation of the reticulocyte count, and only a slight improvement in the blood picture.

Liver extract (Ext. Hepatis Liq. B.P.) in doses derived from 480 gm. daily for twenty-seven days was followed by definite but slow improvement, but complete remission was not obtained until raw liver (240 gm. daily) and liver extracts had been continued for several months.

Days of observation.	R.B.C. $\times 10^6$ .	Hb. %.	Reticulocytes %.	Treatment.
1	1.76	43	3.6	None.
3	—	—	2.0	"
5	1.38	42	1.8	Yeast extract (M.R.C. process) from 480 gm. orally.
7	1.50	40	1.2	" " "
9	—	—	5.6	" " "
10	1.48	44	7.0	" " "
12	—	—	4.6	" " "
14	1.93	49	4.2	" " "
17	1.69	50	5.2	None from 15th to 18th.
19	1.92	48	4.8	Yeast extract (M.R.C. process) from 100 gm. intramuscularly.
21	1.96	48	1.4	" " "
23	—	—	3.6	" " "
25	2.06	54	0.8	" " "
28	1.81	48	0.8	None from 26th to 32nd.
32	2.22	50	1.8	Alcoholic extract (nainsook method) from marmite 120 gm.
34	—	—	2.4	" " "
37	2.17	59	2.8	" " "
40	—	—	1.0	" " "
44	2.38	60	0.4	Liver extract (B.P.) from 480 gm.
70	3.09	65	—	" " "

Case 23. *Slight response to alcoholic extracts of yeast, with no evidence of increased potency after autolysis.* J. M., male, aged 56, suffered from pernicious anaemia of two years' duration. There was slight neurological involvement. He had always eaten meat on six days a week, and plenty of green vegetables. Gastric analysis showed a histamine-refractory achlorhydria with only a trace of pepsin (less than 4 units, Fuld).

The administration of a 65 per cent. alcoholic extract derived from 480 grm. of fresh brewer's yeast daily for ten days was accompanied by a small reticulocyte response which reached 7.0 per cent. on the eleventh day. The haemoglobin increased by 10 per cent. during this time, but there was no significant change in the red-blood cell count. Subjective improvement was slight.

For the next ten days he was given similar doses of a 65 per cent. alcoholic extract derived from the same batch, but which had been allowed to autolyse for seven weeks before extraction. There was no definite secondary reticulocytosis, and no significant increase in the rate of blood regeneration. There was, therefore, nothing to indicate that autolysis had brought about any increase in potency.

Liver extract B.P., derived from 480 grm. daily, produced a second reticulocyte response, reaching 10.4 per cent. on the seventh day, and a more rapid rise of red-blood cells and haemoglobin than had occurred with the yeast extracts.

Days of observation.	R.B.C. $\times 10^6$ .	Hb. %.	Reticulocytes %.	Treatment.
1	1.26	34	2.6	None.
3	—	—	3.6	"
6	1.27	32	2.4	Alcoholic extract from fresh yeast 480 grm.
8	—	—	3.0	" " "
10	1.34	34	5.2	" " "
12	—	—	6.8	" " "
15	1.34	42	5.8	" " "
16	—	—	7.0	" " "
17	1.37	42	4.8	Alcoholic extract from autolysed yeast 480 grm.
19	—	—	5.8	" " "
21	1.24	44	2.8	" " "
23	—	—	1.0	" " "
26	1.74	49	1.2	" " "
27	—	—	1.8	Liver extract B.P. from 480 grm.
29	—	—	3.4	" " "
31	—	—	3.8	" " "
33	—	—	10.4	" " "
34	1.86	54	3.6	" " "
38	2.03	65	5.5	" " "
44	3.13	77	1.0	" " "

*Case 24. Atypical pernicious anaemia without achlorhydria, responding to an alcoholic extract of fresh yeast, with no evidence of increased potency after autolysis.* J. M., male, aged 35, was admitted to the Royal Victoria Infirmary on 19th May, 1933, suffering from pernicious anaemia, atypical in that free hydrochloric acid was present in the gastric juice. He had generalized seborrhoeic dermatitis, which had been present with exacerbations and remissions for ten years. Six weeks before admission he was noticed to be pale and yellow and had dyspnoea, palpitation, and oedema of the legs. The tongue, which was clean and smooth, had been sore at intervals for ten weeks. Numbness and tingling was present in the hands and feet, but there were no signs of postero-lateral involvement of the spinal cord. Several small retinal haemorrhages were present. The spleen was not palpable. The diet had contained plentiful amounts of meat and green vegetables. Gastric analysis was not performed at once because of his poor general condition. On 20th Nov., 1933, the fasting juice was achlorhydric, but in the secretion obtained an hour after histamine stimula-

tion there was 0.26 per cent. free hydrochloric acid and sixteen units of pepsin (Fuld).

On 19th May, 1933, red-blood cells numbered 0.89 millions per c.mm. with haemoglobin 24 per cent., giving a colour index of 1.3. The erythrocytes showed marked anisocytosis and megalocytosis, and some poikilocytosis. White-blood cells numbered 4,200 per c.mm.

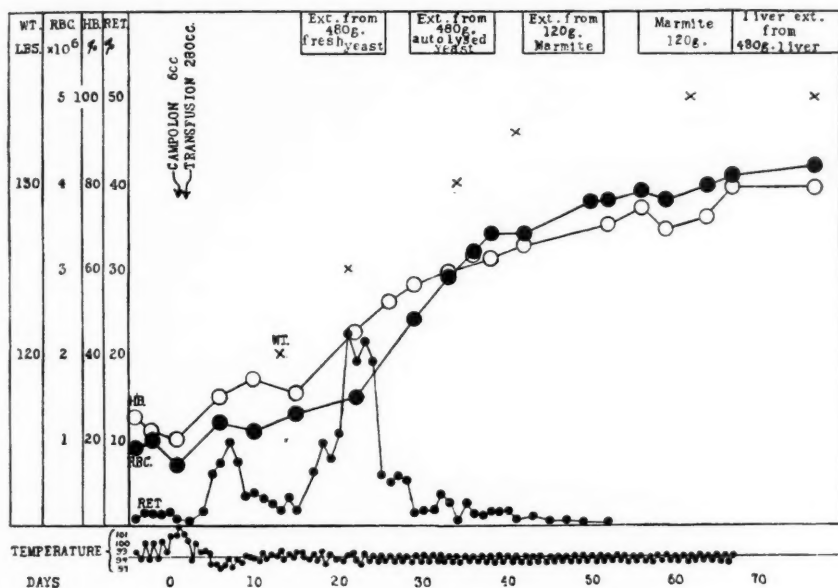


FIG. 2.

On 24th May he received a single injection of Campolon liver extract 6 c.c. (derived from 15 grm. of liver) and was subsequently transfused with 10 oz. of blood. The red-blood cells numbered 1.23 millions per c.mm. with 30 per cent. haemoglobin on the sixth day, and the reticulocytes rose to 9.8 per cent. on the seventh day. Two weeks after the injection the red-blood cell count and haemoglobin percentage had shown no further increase, and the reticulocyte crisis had completely subsided. An alcoholic extract of fresh yeast, was given in doses derived from 480 grm. daily. A rapid rise of reticulocytes occurred, reaching 22.2 per cent. on the sixth day. By the eleventh day red-blood cells numbered 2.57 millions per c.mm., with 52 per cent. haemoglobin.

He was now given an extract prepared from yeast of the same batch, but which had been allowed to autolyse for three weeks before extraction. The red-blood cells and haemoglobin continued to increase, but there was no secondary reticulocytosis or other indication that autolysis had brought about an increase in the potency of the yeast (Fig. 2).

A 65 per cent. alcoholic extract from marmite 120 grm. administered for twelve days brought about a further slight increase in the blood picture, so that on 18th July red-blood cells numbered 3.92 millions per c.mm. with 74 per cent. haemoglobin. The subsequent administration of marmite, 120 grm. daily for twelve days, was not accompanied by much alteration of

this level, while liver extract, B.P., derived from 480 grm., given daily for eighteen days was likewise ineffective, and on 16th August red-blood cells numbered 3.68 millions, with 78 per cent. haemoglobin. Cooked liver, 240 grm. daily, brought the red-blood cell count to normal, but even after the liver had been supplemented by iron ammonium citrate, 6 grm. daily for two months, the haemoglobin was only 82 per cent.

On 20th Nov., 1933, all treatment was discontinued, and he was told to take an ordinary mixed diet. He has remained well since, and on 8th Jan., 1934, red-blood cells numbered 5.0 millions per c.mm., with 92 per cent. haemoglobin.

The rapid gain in weight which occurred during the administration of yeast extracts is shown in Fig. 2.

Days of observation.	R.B.C. $\times 10^6$ .	Hb. %.	Reticulocytes %.	Treatment.
1	0.89	24	0.8	None.
6	0.7	20	0.8	Campolon liver extract 6 c.c. (one injection only).
7	—	—	0.4	Transfusion 300 c.c.
11	1.23	30	7.2	
12	—	—	9.8	
15	1.12	34	3.8	
21	1.31	31	1.8	Alcoholic extract from fresh yeast 480 grm. daily.
26	—	—	22.2	" " "
29	1.5	45	19.0	" " "
34	2.39	56	1.2	Alcoholic " extract " from autolysed yeast 480 grm.
37	—	—	3.4	" " "
41	3.4	62	1.4	" " "
47	3.4	65	—	Alcoholic extract from marmite 120 grm.
57	3.76	70	0.2	" " "
61	3.92	74	—	Marmite 120 grm.
72	4.05	79	—	Liver extract, B.P., from 480 grm.
82	4.24	79	—	" " "
90	3.68	78	—	Whole liver " 240 grm.
102	5.1	88	—	" " "
130	5.01	85	—	Whole liver 240 grm. and iron ammon. cit., 6 grm.
186	5.12	82	—	None.
235	5.00	92	—	"

*Case 25. Inconclusive result with acid autolysate of yeast, and with alcoholic extract of yeast, in a patient previously treated with liver extract.* W. B., male, aged 50, suffered from pernicious anaemia of seven years' duration. He was admitted to the Royal Victoria Infirmary on 27th May, 1933, having relapsed during the past three months due to neglect of liver diet.

Red-blood cells numbered 670,000, with 17 per cent. haemoglobin, and he was given a transfusion of 300 c.c. of blood. As there was no improvement he was given a single injection of 6 c.c. of Campolon liver extract (derived from 15 grm. of liver). The reticulocyte count rose to 29 per cent. on the sixth day and fell to normal by the twenty-first day. The red-blood cells numbered 2.88 millions per c.mm., with 58 per cent. haemoglobin on the twenty-third day, and on the twenty-seventh the count had fallen to 2.34 millions with 54 per cent. haemoglobin.

During the administration of an acid autolysate of yeast, and later of an alcoholic extract of yeast, however, there was no secondary reticulocytosis, and the increase in red-blood cells and haemoglobin which occurred could

have been due to a continuation of the remission induced by the initial transfusion and the single injection of liver extract.

The only conclusion which could be drawn was that while either of the extracts may or may not have possessed some potency, neither was effective to any marked degree.

*Case 26. Negative result with alcoholic extract of yeast given intramuscularly, followed by a response to a similar extract given by mouth.* T. C., male, aged 35, suffered from pernicious anaemia of seven months' duration. He suffered from occasional paraesthesiae, but there were no symptoms or signs of subacute combined degeneration of the cord. The diet had contained plentiful amounts of meat and green vegetables. Gastric analysis after a gruel meal showed achlorhydria, with a low total acidity.

At the commencement of treatment red-blood cells numbered 0.91 millions per c.mm., with haemoglobin 25 per cent., giving a colour index of 1.37. Reticulocytes 1.6 per cent. White-blood cells numbered 2,700 per c.mm.

The injection of alcoholic extract (batch 5) derived from 27 gm. of yeast daily for ten days was without haemopoietic effect. A similar extract (batch 8) given by mouth in doses derived from 480 gm. daily produced a reticulocyte rise commencing on the fifth day and reaching 23.5 per cent. on the seventh day (Fig. 3). There was a marked subjective improvement, and the haemoglobin increased by 10 per cent. in two weeks.

The administration of liver pulp, 240 gm. daily, was followed by a second reticulocyte crisis reaching 30.2 per cent. on the sixth day, and a rapid increase of red-blood cells and haemoglobin.

Days of observation.	R.B.C. $\times 10^6$ .	Hb. %.	Reticulocytes %.	Treatment.
1	0.91	26	3.6	None.
4	—	—	13.0	"
12	0.91	25	1.6	Alcoholic extract from 27 gm. yeast intramuscularly.
21	0.82	28	2.8	" " "
22	—	—	4.4	Alcoholic extract from 480 gm. by mouth.
24	—	—	0.8	" " "
26	0.95	28	7.6	" " "
28	—	—	23.5	" " "
33	1.28	33	9.0	" " "
36	1.26	38	4.8	" " "
37	—	—	4.4	Liver pulp 240 gm.
42	—	—	30.2	"
43	2.04	54	20.6	"
50	3.21	62	2.4	"

*Case 27. Negative result from extracts of marmite, autoclaved and otherwise.* T. H., male, aged 50, suffered from pernicious anaemia with subacute combined degeneration of the cord of twenty months' duration. He had taken small amounts of liver and liver extracts, but none during the past six months. The gastric juice contained no free hydrochloric acid or pepsin, even after histamine stimulation.

At the commencement of treatment red-blood cells numbered 1.86 millions, with 43 per cent. haemoglobin. A 65 per cent. alcoholic extract from autoclaved marmite was given in doses derived from 120 gm. daily for ten days without effect, but the subsequent administration of an extract from marmite of the same batch which had not been autoclaved also failed in this instance to influence blood regeneration.

The red-blood cells and haemoglobin had diminished and the neurological condition had become worse during the latter part of this period. The daily intramuscular injection of Campolon liver extract in doses of 6 c.c.

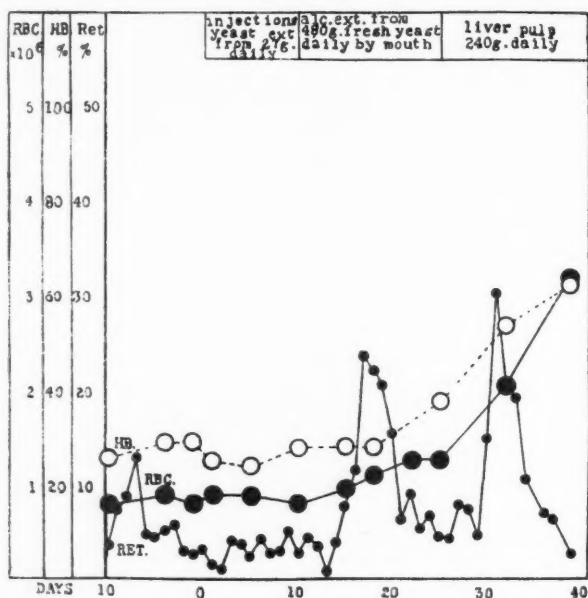


FIG. 3.

(derived from 15 gm. of liver) was followed by a reticulocyte crisis reaching 32.8 per cent. on the sixth day. There was a rapid rise of red-blood cells and haemoglobin, and later a marked improvement in the neurological condition.

Days of observation.	R.B.C. $\times 10^6$ .	Hb. %.	Reticulocytes %.	Treatment.
1	2.0	46	—	None.
3	—	—	0.2	"
5	—	—	0.2	"
7	1.86	43	0.1	Alcoholic extract from autoclaved marmite 120 gm.
9	—	—	0.2	" " "
11	1.66	44	0.2	" " "
13	—	—	0.2	" " "
16	1.29	36	0.2	Alcoholic extract from marmite 120 gm.
19	1.27	30	0.6	" " "
21	—	—	0.2	" " "
24	1.23	22	0.2	Campolon liver extract 6 c.c. daily.
27	—	—	10.0	" " "
29	—	—	32.8	" " "
32	2.33	40	14.4	" " "
52	4.18	67	1.2	" " "

*Case 28. Negative result from marmite and from extra-digested marmite.* S. S., male, aged 59, suffered from pernicious anaemia of two and a half years' duration. There were paraesthesiae in the extremities but no signs of subacute combined degeneration of the cord. The anaemia had relapsed

while taking inadequate amounts of liver extract (extract derived from 120 grm. of liver daily). Gastric analysis showed a histamine-refractory achlorhydria.

At the commencement of treatment red-blood cells numbered 1.26 millions per c.mm., with 27 per cent. haemoglobin. Reticulocytes 1.2 per cent. The administration of marmite in doses of 60 grm. daily for ten days was without effect. Some of the same batch of yeast which had been subjected to a longer period of autolysis was given in similar doses also without effect.

The subsequent response to liver pulp, 240 grm. daily, and later to intramuscular injections of Campolon liver extract, was slow, and it was four months before the red-blood cell count was brought to a normal level.

Days of observation.	R.B.C. $\times 10^6$ .	Hb. %.	Reticulocytes %.	Treatment.
1	1.20	30	3.2	None.
6	1.27	27	6.0	"
9	—	—	1.4	"
11	1.26	27	1.2	Marmite 60 grm.
13	—	—	1.2	"
15	1.09	23	3.4	"
17	—	—	2.0	"
20	1.24	25	2.0	"
23	1.0	27	2.2	Extra digested marmite 60 grm.
25	—	—	3.4	" " "
27	1.05	20	3.6	" " "
30	0.89	22	3.2	" " "
31	—	—	2.6	Liver pulp 240 grm.
33	—	—	2.2	"
35	—	—	5.2	"
37	1.25	26	13.2	Liver pulp vomited.
38	—	—	16.8	Campolon 4 c.c. on alternate days.
47	2.04	40	10.0	" " "
54	2.47	50	5.4	" " "
62	2.43	52	2.2	Campolon liver extract 6 c.c.

*Case 29. Negative result with alcoholic extract of yeast given intramuscularly, followed by a haemopoietic response to the same extract given by mouth.* F. M., male, aged 49, suffered from pernicious anaemia of twenty-eight months' duration. Ataxia and paraesthesiae commenced twelve months before admission to hospital, and there were signs of mild subacute combined degeneration of the spinal cord. The gastric juice contained no free hydrochloric acid and only a trace of pepsin (less than two by Fuld's method), even after the injection of 1 mg. of histamine.

At the commencement of treatment red-blood cells numbered 1.97 millions per c.mm., with haemoglobin 54 per cent., the colour index being 1.37. Reticulocytes 0.4 per cent.

Alcoholic extract (batch 10) from 48 grm. of yeast was given intramuscularly for six days without haemopoietic effect. The temperature rose to 102° F. on the seventh day and remained above normal for another five days. He had a slight sore throat, and as no other cause for the fever was discovered it was presumed to be due to an upper respiratory infection.

On the twelfth day of treatment he commenced to take alcoholic extract (batch 10), derived from 960 grm., by mouth. The reticulocytes rose to 8.8 per cent. on the eighth day, and there was an increase of red-blood cells and haemoglobin.

During the subsequent administration of liver pulp, 240 grm. daily, there was a secondary reticulocyte crisis reaching 11.2 per cent. on the ninth day.

Days of observation.	R.B.C. $\times 10^6$ .	Hb. %.	Reticulocytes %.	Treatment.
1	2.23	59	1.4	None.
5	1.94	53	0.8	"
9	1.97	54	0.4	Alcoholic extract from 48 grm. yeast intramuscularly.
11	—	—	1.6	" " "
13	1.79	58	1.6	" " "
15	1.76	53	3.5	None.
18	1.43	45	2.2	"
20	1.76	42	2.0	Alcoholic extract from 960 grm. yeast by mouth.
22	—	—	3.4	" " "
25	1.61	50	4.0	" " "
27	—	—	8.8	" " "
29	2.07	50	4.8	" " "
31	—	—	5.8	None.
33	2.51	57	1.4	Liver pulp 240 grm. (commenced 32nd day).
36	—	—	3.4	" " "
40	—	—	11.2	" " "

*Case 30. Negative results with both fractions obtained by lead acetate precipitation, given intramuscularly.* W. W., male, aged 62, suffered from pernicious anaemia of two years' duration. There were transient paraesthesiae, but no symptoms or signs of subacute combined degeneration of the cord. The diet had been deficient in meat, which he disliked. The gastric juice contained no free hydrochloric acid or pepsin, even after histamine stimulation.

At the commencement of treatment red-blood cells numbered 1.79 millions per c.mm., with 43 per cent. haemoglobin, the colour index being 1.20. Reticulocytes 0.4 per cent. White-blood cells numbered 2,900 per c.mm.

Days of observation.	R.B.C. $\times 10^6$ .	Hb. %.	Reticulocytes %.	Treatment.
1	1.67	49	0.8	None.
7	1.44	44	1.0	"
9	1.79	43	0.4	Yeast fraction not precipitated by lead acetate, extract from 200 grm. by injection.
13	—	—	1.8	" " "
15	—	—	5.4	" " "
16	1.62	40	2.0	" " "
17	—	—	2.9	Yeast fraction precipitated by lead acetate, extract from 300 grm. by injection.
19	—	—	3.6	" " "
21	1.27	40	4.8	" " "
23	1.45	41	5.0	" " "
24	—	—	3.6	Campolon 2 c.c. (from 5 grm. liver) daily.
26	—	—	8.8	" " "
28	—	—	18.4	" " "
30	—	—	20.2	" " "
32	2.27	59	10.6	" " "

The yeast fraction not precipitated by lead acetate was administered intramuscularly in doses derived from 200 grm. daily for eight days without

haemopoietic effect. The fraction precipitated by lead acetate was next given intramuscularly in doses derived from 300 gm. daily for seven days, and again the effect was negative.

The subsequent response to liver extract (Campolon) in doses of 2 c.c. (derived from 5 gm.) daily was satisfactory, the reticulocyte count reaching 20.2 per cent. on the seventh day, with a rapid rise of red-blood cells and haemoglobin.

*Case 31. Small reticulocyte rise, but otherwise negative result with fraction obtained by complete alcoholic precipitation of yeast extract.* W. P., male, aged 60, suffered from pernicious anaemia of two and a half years' duration, with paraesthesiae and ataxia during the previous eighteen months. The evidences of postero-lateral involvement of the spinal cord were slight. The diet had been somewhat deficient in meat during the past two and half years. He had taken desiccated stomach for three months, commencing in August 1932, but no potent material of any kind during the past three months. Gastric analysis showed a histamine refractory achlorhydria, with only a trace of pepsin (less than four units by Fuld's method).

At the commencement of treatment red-blood cells numbered 1.89 millions per c.mm., with 46 per cent. haemoglobin, the colour index being 1.22. White-blood cells numbered 3,900 per c.mm.

The fraction obtained by complete alcoholic precipitation of the 65 per cent. alcoholic extract of yeast was administered in doses derived from 1,920 gm. of yeast daily. There was a slight reticulocyte rise reaching 6.2 per cent. on the tenth day, but the result was otherwise negative. The subsequent response to liver extract, B.P., derived from 960 gm. daily was satisfactory.

Days of observation.	R.B.C. $\times 10^6$ .	Hb. %.	Reticulocytes %.	Treatment.
1	—	—	0.8	None.
2	1.98	46	1.6	"
4	—	—	0.6	"
6	1.89	46	0.4	Alcoholic precipitate of alcoholic extract from 1,920 gm. yeast.
8	—	—	1.0	" " "
11	1.78	52	1.4	" " "
13	—	—	3.8	" " "
15	1.47	40	6.2	" " "
17	1.81	48	3.2	Liver extract B.P. from 960 gm.
19	—	—	5.2	" " "
22	2.01	53	9.2	" " "
23	—	—	14.2	" " "
26	2.61	63	5.0	" " "

### Discussion

1. *65 per cent. alcohol-soluble fraction of marmite.* As previously reported (28) the administration in doses derived from 120 gm. of marmite daily was followed by a moderate response in one patient (Case 19), and a good response in another (Case 20), both being examples of classical pernicious anaemia. Subsequent experiences have been less satisfactory. In a third patient (Case 21) in whom osteoporosis with brittle bones was associated

with a blood picture characteristic of pernicious anaemia and a histamine-refractory achylia, the extract produced a small haemopoietic response. An attempt to simplify the process of extraction by confining the marmite to a nainsook bag resulted in a preparation much paler in colour which, in Case 22, was without effect upon blood regeneration. In addition to a fraction derived from autolysed yeast, ordinary marmite contains vegetable extracts, but it was clear that these latter were not responsible for the haemopoietic effect because unflavoured marmite was equally potent (Case 20).

An endeavour to determine the effect of autoclaving upon the potency of marmite in Addisonian pernicious anaemia did not prove successful. In Case 27 neither extract from autoclaved marmite nor extract from ordinary control marmite produced any effect. Other workers (23, 35) have shown that the extrinsic factor in autolysed yeast is not readily destroyed by autoclaving.

2. *Comparison of the potency of yeast extracts for blood regeneration in pernicious anaemia with their vitamin B<sub>2</sub> potency as tested in rats.* The possible relationship of vitamin deficiency to megalocytic anaemias (28) and to sub-acute combined degeneration of the cord (25) has already been discussed. The recent work of Hutter, Middleton, and Steenbock (15) is of interest in this connexion in that it suggests a relationship between vitamin B deficiency and the atrophic tongue.

In a case of classical pernicious anaemia (Case 20), two vitamin B<sub>2</sub> concentrates derived from baker's yeast by lead acetate precipitation gave only slight reticulocyte responses compared with that obtained from an alcoholic extract of marmite (Fig. 1). Peters and O'Brien, who prepared the vitamin concentrates and have tested the alcoholic extract of marmite in rats for B<sub>2</sub> effect, think that there was little difference between the amount of vitamin B<sub>2</sub> administered daily in the second concentrate and that in the extract of marmite. There was, therefore, no parallelism between vitamin B<sub>2</sub> potency and haemopoietic effect, and it seemed that the factor in marmite effective in Addisonian pernicious anaemia was not vitamin B<sub>2</sub>.

Since these experiments were first reported (April 1933), Wills (35, 37) has published independent observations which demonstrated that the factor in marmite effective in tropical macrocytic anaemias is not vitamin B<sub>2</sub>, and that egg-white, although rich in vitamin B<sub>2</sub> is not effective in Addisonian pernicious anaemia when incubated with normal gastric juice. More recently Diehl and Kühnau (6) reported three cases of pernicious anaemia treated with a purified vitamin B<sub>2</sub> preparation, which had been exposed to the influence of normal gastric juice. A small rise of reticulocytes occurred on the fourth or fifth day, and a slight increase of thrombocytes, but there was no increase in red-blood cells or haemoglobin. During the administration of the vitamin B<sub>2</sub> alone not even the slightest reticulocytosis was noticeable.

It may be mentioned also that the 65 per cent. alcohol-soluble fraction of fresh brewer's yeast, the haemopoietic effect of which has been noted above, showed very little vitamin B<sub>2</sub> activity when tested in rats.

3. *The autolysis of yeast.* The unsatisfactory results obtained with dried yeast (28) and with extracts of non-autolysed baker's yeast (Case 20) were in contrast to the efficacy of marmite, which is an extract prepared from brewer's yeast after autolysis with salt-solution. This suggested that potent material might arise during the process of autolysis, perhaps from the activation of the extrinsic factor by an enzyme thus liberated from the yeast.

At the suggestion of Professor Peters experiments were carried out with a batch of fresh brewer's yeast, half of which was subjected immediately to extraction with 65 per cent. alcohol, while the remainder was allowed to autolyse at about 25° C. for several weeks and subsequently extracted in a similar manner. In each of the two cases (Cases 23 and 24) there occurred a haemopoietic response to the extract of non-autolysed yeast in doses derived from 480 grm. daily, but the subsequent administration of extract of autolysed yeast in similar doses was not associated with a secondary reticulocytosis, nor with any other indication to suggest that autolysis had brought about an increase in anti-anaemic potency.

Autolysis with one-fiftieth normal hydrochloric acid, according to the process described by Herron and McElroy (12), which was said to have greatly increased the potency of liver for blood regeneration in pernicious anaemia, was applied to fresh brewer's yeast (Case 25) but the result was inconclusive. In Case 28 neither ordinary marmite nor marmite allowed to autolyse for more than twice the usual period had any effect upon blood regeneration. The results obtained with extracts derived from 480 grm. of fresh brewer's yeast were no better than those obtained with smaller doses of a commercial extract of autolysed yeast (marmite 120 grm. or fractions derived from this amount). It would not be correct, however, to conclude that autolysis had brought about an increase in potency, because marmite is itself an extract and the doses of material administered must be compared in terms of the amount of yeast from which they were originally derived.

Wills (36) suggests that dried yeast, which is ineffective in tropical macrocytic anaemias, may be resistant to gastric digestion. It is possible that in such anaemias the 65 per cent. alcohol-soluble fraction of fresh brewer's yeast would produce results comparable to those which follow the administration of marmite.

4. *Alcoholic extracts of fresh (non-autolysed) yeast.* The administration of a 65 per cent. alcoholic extract of fresh brewer's yeast in doses derived from 480 grm. daily was associated with a reticulocyte crisis of greater or less degree in three out of four cases of pernicious anaemia, including the two mentioned in the preceding paragraph. One case (Case 24) was atypical in that free hydrochloric acid was found subsequently in the gastric juice:

in this instance there was a good reticulocyte response with a rapid rise of red-blood cells and haemoglobin, together with marked subjective improvement and a considerable gain in weight. In two cases of classical pernicious anaemia (Cases 23 and 26) the haemopoietic responses which occurred were submaximal, while in another (Case 25) the result was inconclusive.

Attempts have been made to fractionate further the 65 per cent. alcoholic extract of fresh brewer's yeast. The fraction obtained by precipitating completely with absolute alcohol and rejecting the filtrate gave negative results in Case 31. This fraction was separated into two parts by means of lead acetate, and both fractions gave negative results when given intramuscularly in doses derived from 200 and 300 grm. (Case 30). In further tests the alcoholic extracts of yeast, and the fractions derived from them, will be incubated with normal gastric juice before administration, in order to demonstrate the presence or absence of Castle's extrinsic factor.

5. *Parenteral administration of yeast extracts.* As already mentioned (28), it seemed possible that in addition to the extrinsic factor there might exist in yeast small quantities of a substance resembling the liver active principle. To investigate this possibility it was necessary to avoid contact with traces of intrinsic factor which might be present in the gastric juice of a proportion of patients with classical pernicious anaemia, and to determine whether or not yeast products, effective when given by mouth, would be potent when administered by other routes. The following substances have been given rectally or intramuscularly:

(i) The 65 per cent. alcoholic extract of marmite is unsuitable for intramuscular injection. Given rectally in doses derived from 240 grm. daily this extract gave negative results (Case 19) but not all the material was retained, and the dose had to be omitted on three out of ten days owing to vomiting and toxic symptoms. It was subsequently effective by mouth in doses derived from 120 grm.

(ii) The Medical Research Council process for liver extract (17), when applied to yeast, yielded a yellow powder, which, administered orally in doses derived from 480 grm. of yeast produced a reticulocyte crisis of only 7 per cent. from an initial red-cell level of 1.4 millions per c.mm. When after suitable manipulation the extract was injected intramuscularly in amounts derived from 100 grm. daily the result was negative (Case 22).

(iii) A batch of 65 per cent. alcoholic extract of fresh brewer's yeast was prepared, and part of it was filtered sterile and found to be suitable for intramuscular injection. During the period of oral administration in one case no conclusive result was obtained up to the time when it was necessary to interrupt the experiment. When administered intramuscularly in doses of 10 cc. (derived from 27 grm.) daily to another patient (Case 26) the effect was negative, although a fresh batch given by mouth in doses derived from 480 grm. daily was positive.

In Case 29 the intramuscular injection of 10 cc. of alcoholic extract of yeast (derived from 48 grm.) daily had no effect, while the same batch

given orally in doses derived from 480 grm. daily gave a positive although submaximal response.

The difficulty has been to reduce the bulk sufficiently to enable the extract to be given parenterally in doses derived from adequately large amounts of yeast. Attempts were made to fractionate further the alcoholic extract of yeast, and in Case 30 it was possible to administer intramuscularly amounts derived from 200 and 300 grm. daily. Again the results were negative.

With regard to the possibility that the preparations used might contain small quantities of a substance resembling 'liver active principle', it is significant that liver extracts effective by the oral route are usually at least thirty times as potent when given intramuscularly, and moreover that such extracts can influence blood regeneration when given per rectum (13, 20). On the other hand, yeast preparations which were effective by mouth gave negative results when administered by other routes, and for this reason it is unlikely that they contain significant amounts of a substance resembling liver active principle.

With regard to the presence of a breakdown product of the extrinsic factor, it has been shown that the haemopoietic principle is present in extracts from fresh brewer's yeast, and that autolysis does not noticeably increase potency. The results, taken in conjunction with the evidence already put forward (28), therefore confirm the view of Davidson (5) and others that the effect of yeast preparations in pernicious anaemia is due to Castle's extrinsic factor, which presumably interacts with traces of intrinsic factor in the patient's gastric juice.

It seems probable that many cases of pernicious anaemia, although associated with a histamine-refractory achylia, may retain their ability to secrete small amounts of intrinsic factor in the gastric juice, and that a haemopoietic response to yeast is an indication of this functional activity on the part of the stomach.

Castle and his co-workers (2) have shown that the secretion of intrinsic factor does not necessarily run parallel to that of free hydrochloric acid, pepsin, &c., a fact which probably explains why, in this series, there is no true correlation between the degree of response to yeast and the findings on gastric analysis.

Including those previously described (28), twenty-three cases of megalocytic hyperchromic anaemia have been treated with preparations of yeast or wheat germ. In two patients (Cases 10 and 24) who retained their ability to secrete free hydrochloric acid, the response to yeast was rather better than that usually obtained in achlorhydric pernicious anaemia. The only patient in whom there was a haemopoietic response definitely attributable to wheat germ also had free hydrochloric acid in the gastric juice. Of sixteen patients with complete achlorhydria receiving yeast or wheat germ by mouth ten showed some haemopoietic response. Pepsin was estimated (by Fuld's edestin method) in fourteen cases. In Case 24, which

responded well to yeast, the gastric juice contained 0.26 per cent. free HCl and sixteen units of pepsin. Of the others four had no pepsin, and the remainder had traces only (less than four units). There was no significant difference between the response to yeast in those cases without pepsin and in those with traces of peptic activity. The gastric secretion of total chlorides after histamine stimulation was estimated in five cases; there appeared to be no correlation between this function and the response to yeast.

The excellent response to yeast in Case 20 suggested that in spite of a histamine-refractory achlorhydria the gastric juice contained distinct amounts of intrinsic factor. Pending an opportunity to test this fact by biological assay, a further gastric analysis was performed a year after the commencement of treatment, but the secretion was scanty and there was no return of free hydrochloric acid. In a patient who responded excellently and remained well for 435 days on 45 grm. of marmite daily, Davidson (5) similarly found no return of the ability to secrete free hydrochloric acid or pepsin, and he was unable to demonstrate the presence of intrinsic factor.

In those cases of megalocytic hyperchromic anaemia in which the response to yeast is marked, it is likely that causes other than deficient secretion of intrinsic factor have contributed to the development of the syndrome. Such causes include deficient intake of extrinsic factor, destruction, or defective absorption of the product of interaction of the extrinsic and intrinsic factors, interference with storage in the liver and elsewhere, and increased demands for the haemopoietic material, as by the foetus in pregnancy. Conversely, when such factors operate, the oral administration of yeast is particularly worthy of trial not only for its therapeutic value, but as a test which may throw light on the aetiology of the condition by indicating the presence or absence of intrinsic factor.

*Inadequate intake of certain food substances.* In the tropical macrocytic anaemias (34) in which dietary deficiency is an outstanding feature and the secretory ability of the stomach as tested by gastric analysis is often unimpaired, yeast in the form of marmite is as effective as liver extract. To a lesser extent dietary anomalies may contribute to the deficiency of haemopoietic material in other varieties of megalocytic anaemia, including Addisonian pernicious anaemia.

Of fifteen cases of pernicious anaemia in this series in which the necessary enquiries were made, it was elicited that six had taken a diet deficient especially with respect to meat and green vegetables, and that the remaining nine had taken an apparently normal diet. A response to yeast or wheat germ occurred rather more frequently among those in whom the diet had been defective, but because of the small number of cases the difference could not be considered significant.

*Dysphagia* may lead to a deficient intake of certain foods, especially meat. Obstruction at the pharyngo-oesophageal junction was no doubt a contributory factor in one patient who developed pernicious anaemia without achlorhydria, and showed a moderately good response to marmite (Case 10).

*Defective absorption or destruction of the products of interaction of the extrinsic and intrinsic factors.* The megalocytic hyperchromic anaemia sometimes found in idiopathic steatorrhoea (32) and in sprue (3) often responds well to yeast, and one may look forward to similarly good results in those rare instances of pernicious anaemia complicating intestinal stenosis (7, 14, 18, 21), multiple intestinal anastomoses (2, 16), and gastro-colic fistula (8). In such cases there is probably destruction or deficient absorption from the intestine of the potent material which has been formed higher up in the gastro-intestinal tract. Gastric acidity may be normal, while the presence of intrinsic factor has actually been demonstrated in one instance (21) and its return after treatment in another (2). Some cases of diboethiocephalus latus anaemia may fall into this category also.

Prolonged diarrhoea may have been a factor in the production of pernicious anaemia in Case 15, in which there was a fair response to marmite.

Interference with the storage of haemopoietic principle has been suggested as the cause of a macrocytic anaemia sometimes found in association with disorder of the liver (Wintrobe and Shumacker (38)). Free hydrochloric acid was present in six out of ten cases in which gastric analysis was performed. Spontaneous blood remissions occurred in several cases. A clear-cut response to liver extract was not observed in three instances, but in a fourth a maximal response of reticulocytes occurred. Further light might be thrown on the aetiology of such cases by noting the presence or absence of a haemopoietic effect from yeast.

In pregnant women the demands of the foetus for haemopoietic material, often together with dietary deficiencies, may contribute to the production of pernicious anaemia, even in the absence of achlorhydria. The tropical macrocytic anaemia of pregnancy responds well to marmite (34), but it remains to be seen whether or not yeast will give good results in the somewhat rare examples of the disease which occur in temperate climates.

By administering, to patients suffering from pernicious anaemia, material incubated with normal gastric juice, the presence of the extrinsic factor has been demonstrated, not only in muscle meat and in autolysed yeast, where it exists in approximately twenty times the concentration found in beef muscle, but also in rice polishings and wheat germ (1). The work of Singer (22) indicates that whole hen's eggs may contain small amounts of this substance. With regard to its presence in animal tissues, it is noteworthy that the potency of liver extract is increased by incubation with sources of the intrinsic factor such as gastric juice (11) or stomach tissue (9, 33), and moreover, that if liver extract is rendered inert in pernicious anaemia by hydrolysis with dilute sulphuric acid, the hydrolysed material can be rendered again active by incubation with normal gastric juice (1). The observations in this and in my previous communication (28) confirm the presence of the extrinsic factor in wheat germ, and indicate that it exists in fractions derived from fresh yeast as well as in yeast which has undergone autolysis.

The neurological complications of pernicious anaemia do not respond to yeast and wheat germ even in very large doses. It is probable that the mechanism responsible for the development of subacute combined degeneration of the cord closely resembles that which gives rise to pernicious anaemia, and each is the result of a nutritional deficiency conditioned by a gastric defect (26, 30). It does not follow that both conditions arise from lack of the same substance, and indeed there is evidence that in liver and in brain the factor beneficial to the neurological phenomena is distinct from that which influences the regeneration of blood (27). Such a hypothetical neural factor may resemble the haemopoietic principle in being a resultant of the interaction of extrinsic and intrinsic factors. If so the conditions which determine that one patient suffers from pernicious anaemia alone, while another develops subacute combined degeneration also, might depend either upon extrinsic differences (i.e. in their diet) or upon intrinsic differences (postulating a separate intrinsic factor).

An investigation of the dietary history of cases of pernicious anaemia with and without postero-lateral involvement of the cord has so far failed to bring to light any points of difference in the two groups. On the other hand, the high incidence of subacute combined degeneration of the cord in cases of pernicious anaemia associated with extensive gastric lesions such as polyposis (31), together with its extreme rarity in those varieties of pernicious anaemia, enumerated above, in which factors other than gastric defect contribute largely to the production of the syndrome, have suggested that the neurological condition might be due to a gastric secretory deficiency greater than or different from that which occurs in cases of pernicious anaemia without nervous involvement. If such a difference exists, it is not revealed by the methods of testing gastric function so far employed. In a series of cases of pernicious anaemia with and without postero-lateral involvement of the spinal cord, estimations of pepsin, chlorides, &c., in the gastric juice after histamine stimulation showed no points of difference (31). Figures regarding the haemopoietic effect of yeast in patients with subacute combined degeneration of the cord are available in only four cases, of whom two responded and two did not. These data, although meagre, do not differ materially from those obtained in uncomplicated pernicious anaemia, and suggest that the defect in secretion of haemopoietic intrinsic factor is not necessarily more complete in cases with subacute combined degeneration than it is in those without nervous involvement.

#### *Summary and Conclusions*

1. In order to avoid contact with traces of intrinsic factor possibly present in the gastric juice of cases of Addisonian pernicious anaemia, yeast products which influenced blood regeneration when given orally were administered by other routes. The negative results of parenteral therapy under such conditions supported the hypothesis that the haemopoietic effect of yeast was

due, not to a substance resembling liver active principle, but to the extrinsic factor of Castle.

2. The factor was present in the 65 per cent. alcohol-soluble fraction of fresh (non-autolysed) brewer's yeast. Autolysis did not noticeably increase the potency of yeast for blood regeneration in pernicious anaemia.

3. There was no parallelism between the vitamin B<sub>2</sub> potency of yeast extracts as tested in rats and their effect upon haemopoiesis in pernicious anaemia.

4. Including the previous series, eighteen patients with Addisonian pernicious anaemia have received yeast or wheat germ by mouth, and ten of them have shown some haemopoietic response.

5. Many cases of pernicious anaemia, although associated with a histamine-refractory achylia, may retain the ability to secrete intrinsic factor and a haemopoietic response to yeast is an indication of this functional activity on the part of the stomach.

6. There was no correlation between the secretion of intrinsic factor, as indicated by the haemopoietic response to yeast, and the secretion of acid, pepsin, or chlorides, as determined by gastric analysis after histamine stimulation.

7. In those cases of megalocytic hyperchromic anaemia in which the response to yeast is marked, it is probable that causes other than deficient secretion of intrinsic factor have contributed to the development of the syndrome. The value of the observations upon the haemopoietic effect of yeast in elucidating the aetiology of such anaemias is discussed.

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CHRONIC ULCERATION OF THE COLON<sup>1</sup>

BY EDMUND I. SPRIGGS

(From Ruthin Castle)

With Plates 25 to 32

AN exercise for the physician, which time seldom allows him to enjoy, is to write down his views and impressions of a disease, and then to analyse the records of cases he has treated. The facts may be less dramatic, though more convincing, than the impressions, but the comparison will always be instructive. If the inquiry extends over a number of years, a minor interest is to trace how far this or that treatment, proposed by enthusiastic advocates, has been surrendered to, resisted, or fairly tested.

In the following pages is set forth the writer's experience of ulceration of the colon as seen in this country, illustrated by data from a series of cases in one private hospital for eighteen years up to 1932. Cases seen since or seen in other hospitals or in consultation have contributed naturally to the opinions and conclusions expressed, but are not included in the figures given. Excellent statistical papers on the subject are to be found in the literature. A review of a small number of personal cases, observed in fairly constant circumstances, may perhaps be not less profitable than that of large numbers recorded by others.

The paper is essentially a summary; but the sections upon radiology, in collaboration with Mr. O. A. Marxer, and upon treatment are detailed. Under the heading of prognosis the results of a complete 'follow up' of the forty-eight cases are given.

The organic general inflammations of the colon commonly met in practice are catarrhal colitis, colitis gravis, ulcerative colitis, and chronic ulceration following amoebiasis.

Catarrhal colitis is of two types. The first is chronic mucous or mucomembranous colitis. This may begin with an acute colitis, but its common cause is chronic constipation combined with a nervous tendency and the misuse of purges. It is regarded as mainly a functional disorder, and is classified here among the inflammations mainly for clinical convenience; its nomenclature and the symptoms, course, and treatment have been discussed in a former paper (32).

The second form of catarrhal colitis is an acute or subacute colitis, probably from a massive infection ingested with food, or a chronic infection

<sup>1</sup> Received June 5, 1934.

perhaps carried by the blood, which becomes active through a lowering of resistance, as from chill, exhaustion, or vitamin deficiency. The chief symptom of acute catarrhal colitis is a profuse diarrhoea of rapid onset, accompanied by griping, weakness, and collapse, which vary with the severity of the attack. If there is also gastro-enteritis there is vomiting and earlier exhaustion. The bouts of diarrhoea and vomiting, often met with in practice from unsuitable or contaminated food, come under this heading. Such an acute attack may lead to colitis gravis, but as a rule is less serious from the point of view of the colon than are milder bouts of diarrhoea which recur on and off for months. These may be the beginning of a colitis which goes on to an ulceration which can cripple the life of the patient or bring it to an end. Any such unexplained recurrent diarrhoea should suggest further examination in order that a diagnosis may be made, and suitable treatment applied before a more intractable complaint has developed.

The term *colitis gravis* (Fuld, 12) I use for an active inflammation of the lining of the colon, which is seen with the sigmoidoscope to be red and swollen, bleeding easily wherever it is touched. There may be, and probably is, erosion or ulceration in the unseen and longer parts of the bowel, but general inflammation rather than an ulcer or group of ulcers is the main feature. The symptoms are those of a severe colitis, namely, frequent motions containing mucus and blood, flatulence, and fall in weight and strength. The illness may run its course in a few weeks or months, with pain, sickness, fever, and rapid pulse, but more often abates or becomes chronic. There is no clinical difference between this disease and the acuter stages of ulcerative colitis. The fact that in the latter ulcers may be visible on the inflamed lining of that part of the bowel which is reached by the sigmoidoscope does not justify a separate nomenclature. The term *colitis gravis* in this paper includes, therefore, the severer cases of ulcerative colitis. With the passing of an acute stage, more localized ulceration remains, with lessening of the inflammation of the mucous membrane between the ulcers. Klose (22), in an admirable paper published in 1926, proposed that ulcerative colitis should be called '*colitis gravis chronica*'.

#### *Ulcerative Colitis and the Ulceration of Chronic Amoebic Dysentery*

Cases of chronic ulceration of the colon as they occur in practice in this country may be due to either of these diseases: for the ulcerative colitis which may develop as a late sequel of chronic amoebiasis becomes in time very like the non-amoebic form. Thirteen cases here included are of that nature. Of these five at least had been treated for long periods before admission without knowledge of the amoebiasis. Such a late discovery of amoebiasis occurs from time to time, as in similar cases recently recorded by L. P. Garrod. In others the former infection was known, and repeated courses of specific treatment had been given before admission.

In the following pages in many instances the cases of ulcerative colitis and those of severe chronic ulceration following amoebiasis are, on clinical grounds, classed together. In other instances they are mentioned separately. I hope that the text is in all parts clear in this respect.

Late cases of ulceration of the large bowel secondary to carcinoma or complicating endocarditis, nephritis, or other general diseases are not discussed in this paper.

### *Incidence*

The *proportion of cases of ulcerative colitis* was about five in a thousand admissions. Kantor (21), in a review of 2,500 private patients in America, all, however, with digestive troubles, reported nine in a thousand.

The *ages* of the 35 patients with ulcerative colitis ranged from 21 to 69 years, the average for the 22 men being 48 and for the 13 women 40 years. The history of bowel disturbances, which appeared to be of a similar nature to, though sometimes milder than, the present illness, ranged from a few weeks to as long as 34 years, the average length of such a history in the 35 patients being just under 9 years; hence the average *age of onset* of disorder of the colon was in the thirties for the women and the forties for the men.

The age at onset of the amoebic cases depends upon the time of exposure to infection. Some gave a history of the first attack going back as far as 9, 16, 28, and 31 years respectively. In the others the length of history varied from three months to four years. Eleven of the 13 cases had contracted the disease abroad. Of these the symptoms in 2 came on after visits for health to Egypt and Southern India respectively; and in 1 after a visit to America.

Analysis of the *family history* in most of these patients shed no light upon the incidence. No one complaint, and no bowel complaint occurred more than once or twice among the relatives, with the exception of one family, of which out of three brothers and one sister, living in separate homes, two brothers and the sister have been under treatment for ulcerative colitis at different times.

The rarity of family association, as Bagen (3) points out in a review of 693 cases, 'would argue against the idea that the disease might be contagious'.

*Personal medical history and associated diseases.* It is striking that very few of the patients, excluding those with amoebiasis, had a clean bill of health apart from the ulceration of the colon. Five only gave a straightforward history of gradual looseness, then intermittent diarrhoea leading to ulcerative colitis, without previous illness or disorder. One elderly man, with a recto-sigmoid ulcer, who became addicted to opium, may be added.

Of the remaining 42 patients, 14 were the subjects of *local rectal disorders* made up as follows: 5 cases of piles (slight piles are not included); 1 of piles with severe proctitis; and 8 of fistula, abscess, or fissure. Piles and resulting anal lesions are likely, on the one hand, to be provoked by severe

diarrhoea and sometimes by injudicious or ungentle local treatment. On the other hand, the view is expressed that local rectal lesions are the beginning of an ascending ulcerative colitis. In this group, in 7 cases the rectal disorder came before any symptom of ulcerative colitis, and in 7 it arose afterwards.

The other diseases preceding or associated with ulcerative colitis were of great variety, as follows: appendicitis, 6; pneumonia, 5; rheumatic fever, bronchitis (2 after gassing), and asthma or hay fever, 4 each; unhealthy tonsils, heart disease, 3 each; phthisis, pleurisy, neurasthenia, 2 each; also 1 each of nephritis, psoriasis, jaundice, bone disease, sinusitis, septic bullae, and exanthemata. There was 1 case of arthritis.

I have no comparable figures of the incidence of past and present diseases or minor disorders in the average or non-invalid middle-aged population. But it appears that ulcerative colitis nearly always occurred in those who were or had been unhealthy from some other cause. It seems justifiable to say that in the present state of knowledge the best hope for prophylaxis of this disease, and of so many others, lies in attention to hygiene and to any disorders which may arise, not excepting minor ones.

The view has been expressed that cystitis is often caused by spread of infection from the bowel. Ball (2), however, published figures in 1926 showing that the association of pyelitis and cystitis with catarrhal and ulcerative colitis was not common. The present series, so far as it goes, supports that contention, for there was but one case of coexisting cystitis.

### *Symptoms*

The onset in the 35 cases of ulcerative colitis was described as follows:

Diarrhoea (14 with blood) . . . . .	26 cases
Alternating diarrhoea and constipation . . . . .	2 „
Passage of blood, or blood and mucus, without alteration of frequency . . . . .	3 „
Constipation and passage of blood (2 cases of rectal ulcer and 1 of ulceration and tapeworm) . . . . .	3 „
Constipation and passage of mucus and pus . . . . .	1 „

In 5 cases abdominal pain was an additional prominent first symptom; and in 1, with a rectosigmoid ulcer, local pain.

An attack of diarrhoea at the beginning, with profuse watery stools, with or without blood, is often put down to bad food. It may yield to treatment but recurs. Stress is laid upon the inconvenient precipitancy of motions. In others the onset is more gradual and reported as a tendency to frequent motions with a little blood, sometimes bright and often ascribed to piles; or the disease may begin with occasional constipated motions, frequency coming later.

The doctor should insist in every doubtful case upon repeated inspection of motions. This simple step saves valuable time. There may be but little

constitutional disturbance at first, and the danger is that the patient may keep about, doing his work, until ulceration is well established.

For example: A hard-working merchant, aged 43, had suffered for five months from recurrent precipitant diarrhoea, with blood. The symptoms were ascribed to piles, which were present. He had not rested at all. On admission he was the subject of advanced ulcerative colitis, of which, in spite of temporary improvement under various treatments, he died six months later.

The course was usually intermittent. Thus 30 patients had enjoyed remission of symptoms, some for long periods. One, with a history of a first attack twenty-three years before, had filled a hard responsible post for eighteen years when a second attack came on. From this he recovered and was admitted four years later in a third attack, which had lasted three months. Secondary polypi could be seen in the sigmoid. After four months' treatment he appeared well and has remained so for four years.

As the disease progresses remissions tend to cease. Thus, in a case with a thirteen years' history, the passage of blood with the stools had continued for the past four years. Any chill or strain may start one of the recurring attacks. In only 5, the longest with a history of three years, was there continuous progress from the beginning until admission.

Various patients had long been the subjects of 'colitis' or a subacute 'gastro-enteritis', or even, as in one, a lifelong tendency to looseness, before the appearance of blood; but no patient gave a typical 'mucous colitis' history of long constipation with the passage of mucus. And in a large series of cases, under the care of the writer, of mucous colitis and associated disorders classed as functional (32, p. 533) the passage of such cases into ulcerative colitis was not noted, and is certainly infrequent. A recent writer (29) described muco-membranous colitis as a milder form of chronic ulcerative colitis; and this is not the only author who has written of seeing all stages, presumably in the same patient, from chronic constipation, through mucous and membranous colitis, to ulcerative colitis. In the present writer's experience the two forms of colonic disease are of a different order. This is also the experience of others (21, 34). No doubt the lowered resistance of a colon long subject to mucous or muco-membranous colitis might render it more likely to become the seat of ulceration in isolated cases. But this is not the usual history. Ulcerative colitis appears from its course to be an infective disease<sup>2</sup> from the beginning.<sup>3</sup>

<sup>2</sup> The word infective is here used to denote that the disease is probably due to organisms or a virus, in the same sense as that implied in the term 'infective endocarditis'. Some American writers, and, recently, at least one in this country, use the term as implying that a disease is liable to be passed from one person to another. The literal meaning of the word may justify that interpretation; but as a convention it seems desirable to prefer the word infectious, or, in certain cases, contagious, for a disease which is likely to be caught from others.

<sup>3</sup> As another possible factor it may be noted that in experimental avitaminosis the resistance to germs of the lining of the colon, as of other tissues, is lowered.

As regards the *onset* in the 13 amoebic cases, 5 patients noted the passage of blood as a first symptom, associated in 2 with diarrhoea, and 2 with constipation. One case began with diarrhoea and mucus and 1 with diarrhoea after a purge. The other 6 gave only the statement that their complaint began with 'dysentery'.

TABLE OF SYMPTOMS AND PHYSICAL SIGNS

	<i>Symptoms</i>		
	Ulcerative colitis and colitis gravis.	Chronic ulceration after amoebic dysentery.	Both groups.
	35 cases.	13 cases.	48 cases.
Pain	28	8	36
Colicky or griping	12	5	17
Worse before motions	11	—	11
Worse after motions	3	1	4
Worse after food	5	—	5
No pain	7	5	12
Flatulence or abdominal dis- tension (7) complained of in	15	5	20
Distension observed in	4	—	4
Nausea	4	1	5
Vomiting	5	1	6
Fever	16	5	21
Diarrhoea	29	11	40
Constipation (complained of)	4	—	4
Nervousness, depression	11	3	14
Exhaustion	8	3	11
Headaches	4	—	4
Insomnia (severe)	3	2	5
Lethargy	2	2	4
Palpitation	9	—	9
Dyspnoea	3	—	3
<i>Physical Signs</i>			
Tongue clean	17	5	22
" furred	9	2	11
" very dirty	1	1	2
Teeth—pyorrhoea	4	—	4
" apical abscesses	4	2	6
Buccal ulcers	—	1	1
Abdomen:			
nil abnormal	13	4	17
Tenderness	20	6	26
Distension	4	—	4
Rigidity	1	3	4

Forty out of 48 were subject to *diarrhoea*, many of them severely; 10-20 or more stools a day. Many of the stools were mainly, or entirely, mucus and blood, and sometimes mucus only. There might thus be 6 to 9 such motions, and 2 others containing faeces. In the acuter cases there was *precipitancy*. The motions in some are liable to follow food and hot drinks, a clinical demonstration of the gastrocolic reflex. The tendency to intermittency is seen in short periods as well as in long, exacerbations recurring, in which many more motions are passed.

Two patients had not diarrhoea, but one or two loose motions a day. Four complained of constipation, 3 of whom were the subject of ulcers in the pelvic colon and probably not elsewhere. The rate of passage of a barium meal was normal in these, not hurried and not delayed.

*Abdominal pain* was complained of in 36 out of 48 cases. The pain is often colicky or griping, and its relation to motions shows that it occurs with contraction of the diseased bowel. It is often relieved by the motion, but not always; for in 4 patients it was worse afterwards for a time, in none of whom was there an anal lesion, though in one colitis gravis continued into an upper proctitis.

The site of the pain is generally about or below the navel, but, in case of ulceration low in the bowel, it may be in the left lower abdomen or in the rectum.

A second kind of abdominal discomfort occurs in this as in other forms of colitis, namely, an 'indigestion' pain, coming on an hour or so after food in some part of the upper abdomen. In a man with ulceration of the descending colon, pain on the left side of the abdomen continued for an hour after a meal.

My experience is that the absence of pain is not a good sign in ulcerative colitis. Of the 6 in the ulcerative colitis group who did not complain of pain, 4 were severe cases, 2 of them ultimately fatal.

Pain is, however, on the whole a less prominent feature than is the *fall of strength and weight*, as was pointed out by Hale-White (16) and later by Fuld (12). It may proceed to emaciation. It is surprising, however, that a fair appetite and a normal or nearly normal weight may be kept with pronounced symptoms in a few cases; thus 8 patients did not think much weight had been lost.

*Flatulence or distension* was complained of by 20 patients. Seven specially mentioned distension of the abdomen. In 4 of them it was present, and in others was a subjective sensation. *Nausea and vomiting* are distressing symptoms, which may come on with griping and just before a motion.

*Fever* was usually intermittent, coming on with an exacerbation of symptoms and lasting a few days. Continuous fever is of serious import, and was present in the 3 cases who died in hospital, 2 of whom were beyond hope when admitted. A patient with this disease may, however, be dangerously ill without fever.

The *pulse-rate* is, of course, nearly always a valuable guide to the state of the patient. In this series 1 patient who died had a settled high rate of 120 or more. Other fatal cases did not show this except as a terminal state, whilst a rate of 120-130 occurred during severe stages in 3 patients who recovered (18).

The group of 13 cases in which amoebiasis was discovered did not differ materially in their symptoms. Indeed the symptoms are not brought about by the cause of the disease, but by the ulceration of the colon. There were 7 very ill people in this group, though all recovered. Any 'distension' was

subjective. Fever occurred in 5 of the 13 cases for longer or shorter periods. In 3 of them, all of whom were severely ill, it differed in no way from that of cases in the other group, being worse with exacerbations and subsiding between. In the other 2 it was casual, i.e. after emetine, and with a cold on the chest. Eleven of the amoebic cases were diarrhoeic and the other 2 had loose motions. In the early stages of dysentery, blood may appear in a constipated patient without the more usual looseness; a mode of onset which also appears among these histories.

The *nervous* accompaniment of the disease is considerable, the patients becoming depressed and emotional until definite improvement sets in. In this series nervousness and depression, great tiredness, and weakness are often recorded in both groups. In 1 patient any emotional stress at home would be followed by bleeding from the bowel. Headaches were troublesome in 4 cases and insomnia especially in 5. In 4 severe cases, 2 in each group, lethargy or great mental tiredness was prominent; all recovered.

Other constitutional symptoms are palpitation, dyspnoea, and persistently cold extremities. One patient, a young man, had many attacks of paroxysmal tachycardia, as many as 72 bouts in 24 hours. He recovered, and has lived a strenuous life for 9 years since.

#### *Physical Signs*

The *tongue* is often clean, as in 22 patients. In severe cases it is glazed, dry, or red, but was very dirty in 2 patients only. Apical abscesses of the *teeth* were discovered in 5 and pyorrhoea in 4 cases: 7 of these 8 patients were severely ill. Another who recovered had ulcers on the gums, palate, tongue, and fauces, also conjunctivitis. It is perhaps not a coincidence that the dental lesions were found in the worse cases; otherwise the state of the mouth in most was at least as good as the average. The *tonsils* were suspected of disease in 1 only, though 2 others mentioned former tonsillar disease.

In a good proportion of cases examination of the *abdomen* yields surprisingly little information. Thus, in 17 out of the 48 in this series nothing abnormal was observed. Inspection is often negative. General distension, except as a late sign, is rare. Palpation revealed tenderness in just over half the cases. It was right-sided, left-sided, or on both sides in an equal proportion, most often below the navel. In several the tenderness was about the site of ulceration as seen with the sigmoidoscope or indicated by X-ray films; but the correspondence is not close enough, taking all the patients, and there is too much general tenderness in colitis to enable the seat of the lesion to be deduced with any certainty from gentle palpation. The colon is seldom to be felt in ulcerative, as compared with other forms of colitis. Rigidity, like distension, is uncommon, and of serious, but not necessarily fatal, import.

The stools in a typical case are made up of rounded masses of mucus and pus, with pledgets of red, dark-red, or red-brown partly changed blood, amid loose or semiformed faecal matter. In some motions no faeces may be seen. Sometimes formed faecal matter may be passed occasionally, with or between abnormal dejecta. Blood was seen frequently in nearly all. Exceptions were two patients with visible ulcers in the rectum or sigmoid, probably relics of former dysentery, in whose stools no macroscopic blood was observed; also one severe case, ultimately fatal from haemorrhage, in which visible blood was absent from the frequent stools for days at a time, or only spots or streaks would be seen. Mucus is recorded in most of the cases also. Pus is often visible to the naked eye in severe cases. It has been said to be evidence of a secondary infection of the ulcerated area; but if microscopical examination of the faeces be made, pus cells will be found in abnormal numbers. Thus, of the cases of ulcerative colitis in this series there is only one in recent years in which its presence was not recorded at some time, and in most regularly.

The microscopical examination and culture of the faeces needs to be thorough and repeated, search being made for blood and pus cells, the *Entamoeba histolytica*, other parasites and their eggs, the bacilli of dysentery, enteric fever, and of tuberculosis in certain cases; and the coliform and coccal organisms. The blood may also be tested against various bacteria. In 11 cases in this series, the entamoeba of dysentery was found, and in 2 the cysts only.

Lambliæ seemed to be a possible cause or sustainer of the colitis in several, since the symptoms disappeared as the protozoon became scarce under treatment. This is not conclusive, since the douches used against lambliæ would benefit the colitis, but it is suggestive. In one case there was also low ulceration and an anal abscess without diarrhoea. This patient also did well as the organisms disappeared. These parasites are said to live mainly in the duodenum and jejunum; but they diminish in number rapidly in the dejecta when the colon is washed out with methylene-blue solution.

The organisms found in the faeces in these cases were usually *B. coli* and streptococci, sometimes haemolytic (obtained in one case from inflamed tonsils also) and sometimes not, and occasionally *Streptococcus viridans* and *B. proteus*. Cultures from swabs obtained through the sigmoidoscope yielded generally good growths of *B. coli* and cocci, the latter including Gram-positive organisms, other than surface staphylococci, usually diplococci. In a few cases in which a diagnosis of tuberculosis of the bowel had been suggested at some time, acid-fast bacilli, searched for by the special methods, were not found.

In some forms of acute colitis, bacteriological examination of the faeces, checked by blood tests, may determine the cause of the disease and suggest a line of treatment. Such are the acute colitis of bacillary dysentery, pneumococcal, streptococcal, and other severe varieties. In chronic ulcerative

colitis as seen in this country, bacteriological examinations, when all is done, have not yet enabled us to detect different types or given any certain guide in treatment.

The *blood* shows as a rule a secondary anaemia, which may be severe, especially in wasted patients or those with much haemorrhage. A mild polymorphonuclear leucocytosis is common, and in advanced cases a higher count is found. A rapid rise naturally suggests abscess formation in or about the bowel. Over 10,000 white cells to the c.mm. were present in 15 patients, the highest figure being 29,000. Twelve out of these 15 recovered, pus having been evacuated from a rectal abscess in 2 of them. The combination of leucocytosis with severe anaemia is more serious than either of these conditions alone, but recovery may still occur. Conversely in a severe progressive case the haemoglobin may not fall below 50 per cent. or the leucocyte count rise above 10,000 until the final stages.

A Wassermann reaction was found in one case, with small 'punched-out' ulcers in the pelvic colon. The lesions were not thought to be due to syphilis; and were no longer visible after the symptoms had disappeared under treatment, without specific remedies.

In many cases the testing of the *gastric juice* is inadvisable, though in milder ones, as in those of colitis without haemorrhage, it is of value to determine the presence or absence of achylia. In 14 patients in whom the test was made, the results showed superacidity in 8, a normal juice in 3, and subacidity in 3.

The *sigmoidoscope* gives information as to the state of the lower bowel which is got in no other way. It is especially useful in revealing the region of the recto-sigmoid junction, which the finger cannot reach and which is less easy to demonstrate well with a barium enema. The instrument can with experience be passed gently with little disturbance and without an anaesthetic. In a few cases no preparation may be needed; but if much faecal matter be in the lower bowel the view will be obstructed and the procedure in vain. Hence I generally have the bowel washed out first. A quarter of a grain of morphine is then injected under the skin and a cocaine suppository put into the rectum, the examination being made half an hour later. Inflammation of the lining, the presence of superficial, punctate, or larger ulcers, of polypi or of growth can be seen in the lower 20 cm. or more of the bowel. The sigmoidoscope was used in 34 of the patients. The remaining 14 comprised 8 who were too ill to be so examined, and 6 of the amoebic cases in whom the diagnosis was clear enough.

In acute cases the appearance seen is that of colitis gravis, namely, a red inflamed friable mucous lining, bleeding easily when touched, with blood-stained mucus and pus descending from above. Ulcers may, or may not, be present in the part of the bowel which is visible. Thus in 8 of these cases, 7 of which were severe (and none amoebic) the appearance was as above without ulceration. In others the inflamed mucous membrane showed a various extent of ulceration, from those in which there were ulcers over

most of it to one with two ulcers of the size of a sixpence. In the less severe cases the mucous membrane around the ulcer or ulcers may not be much inflamed.

All the above-mentioned appearances are compatible with recovery. Of the 5 patients who died under treatment or within a year afterwards, 3 were too ill to be examined with the sigmoidoscope. Of the other 2, 1 showed an inflamed mucous membrane with yellow patches, and 1 the typical appearance of colitis gravis without ulceration in the sigmoid, but with mucus, pus, and blood coming down from above.

With improvement the mucous membrane becomes less red, and small white or yellow patches can be seen; later there may be a membrane rather greyer than normal and perhaps injected.

The so-called secondary polypi of the colon, which are distorted islands of mucous membrane projecting between the confluent ulcers, occurred in advanced cases. In one, already referred to, their presence did not prevent a recovery from symptoms, which has continued for four years. Two cases of primary polyposis, in which the polyps were separate and clean and the mucous membrane between normal, are not included in this series (1).

### *Radiology*

The photographs shown were taken by Mr. O. A. Marxer, who has collaborated in the following notes.

The existence of severe colitis can often be recognized by a skilled observer on simple screening. The diagnosis is easily confirmed by the use of barium and the site of ulcers seen. It will be understood that in acute stages an X-ray examination is not made.

Ulcers may, of course, be confined to one or two parts of the bowel, especially in earlier or healing stages; but the tendency in the developed form of the disease is for them to spread widely from the caecum to the rectum, the transverse and descending parts being those most likely to escape. The X-ray, when available, can show the affected areas not seen with the sigmoidoscope.

Radiological features usually described as associated with colitis gravis, with or without ulceration, are irregular segmentation, inhibition, and spasm. These are often observed, but are not in themselves proof of ulceration, being seen in other conditions also, and are to be regarded as indirect signs. Modern radiology allows of closer and more delicate observations, particularly of two kinds: (a) the study of finer alterations of the profile of the barium-filled bowel; and (b) the strial pattern or picture thrown by the remains of the barium lying in folds or crevices of the mucous membrane after the lumen is empty. Air distension is of great help in studying these patterns. Such observations, when combined with those of the variations

in the main form and movements of the bowel, give information of the state of the lining which was not formerly available. In early stages there may be no certain X-ray evidence of an ulcer, but an established area of ulceration can be demonstrated both in filling and as a strial pattern.

*Indirect signs.* (i) Exaggerated and frequent mass movements are the main feature in the more severe cases, the bowel being intolerant of its contents. Barium, especially when suspended in buttermilk, is expelled rather less quickly than the chyme of fresh food.

(ii) Irregular segmentation or haustration (Figs. 13, 15) occurs in many conditions and may have little pathological significance. It is, however, a feature of the ulcerated bowel, especially when haustrations are broad and asymmetric. It was observed in 20 cases in this series at some part of the colon, as follows: in a great part or the whole of the colon in 9; in the caecum 8 (5 amoebic); transverse colon 6; splenic flexure 3; sigmoid specially, 6.

The next most common indirect sign, that of (iii) inhibition (Fig. 8) of a part or of the whole of the colon, may be produced in a normal bowel in some circumstances. It is, nevertheless, characteristic of severe colitis, including ulcerative cases. Inhibition was prominent in 15 of these cases, including 8 of the more severe. Irregular segmentation and inhibition may be seen at different parts of the same bowel, as in 7 cases, and sometimes at the same part at different stages.

The appearance of a flattened haustration, bordering on inhibition with or without a visible depression in the profile, should probably be included as an indirect sign. It is seen in the right aspect of the descending colon in Fig. 1, also 13. In the same film are direct signs, to be described below.

Irregular contraction may merge into (iv) spasm. This is defined elsewhere (32, p. 548) as being present if 'a segment of bowel remains contracted, the contents being squeezed out so that the column of material is deformed or interrupted'. Spasm was especially notable in five cases, in three of them associated with inhibition.

(v) Small cut-out or indented appearances are sometimes seen, especially in the sparsely affected intestine, and are placed tentatively among the indirect signs. They may probably occur in the same haustrum as an ulcer, like an incisura opposite a gastric ulcer. In Fig. 1, from a localized chronic case, there is a sharp septal shadow between two of the flattened haustra. (See also arrow in Fig. 13.)

A comparison of the sites of ulceration as gathered from these indirect signs shows that in several cases the X-ray gave a clear indication of the site of disease above the area reached by the sigmoidoscope.

*Direct signs* are (i) gross deformities: severe ulceration causes gross changes in the bowel picture. In chronic cases it may not be possible to recognize the junction of the small and large bowel owing to the obliteration of the caput caeci. A shortening of the bowel also takes place gradually, so that a sigmoid loop can be transformed to a rigid narrow tube. Many examples

have been published of such deformities, including multiple constrictions, and they need not be illustrated here.

(ii) Fine variations in outline: fine jagged irregularities are seen in the transverse colon in Fig. 2. In Figs. 3 and 4 the appearance resembles that of an inverted tray in profile.

(iii) Strial patterns: the pattern of the striae in a normal bowel is shown in Figs. 5 and 6. In the large bowel undue longitudinal striae, as shown in Figs. 8 and 9, are direct signs of colitis. If there is ulceration the craters may be seen, especially with the aid of air distension, barium being held in the edges. No doubt the depth and steepness of the crater margin has a bearing on the width of the visible ring. Three such craters can be seen in the strial pattern of the transverse colon in Fig. 7, and a few in the descending colon in Fig. 8. They have a tendency to be in longitudinal order, and are more likely to be seen if the taenia is shown in profile. A roughened or fluffy outline of the strial pattern of the inhibited bowel, as seen in Fig. 12, is probably due to granulation of the mucosa.

The irregularity in outline associated with ulceration of the colon may become a polypoid pattern, as in Figs. 10 and 11. These are from two cases in which polyps were seen with the sigmoidoscope. A study of plasticine models by Mr. Marxer suggests that the polyp gives a single ring of barium round its base, whereas a round ulcer shows a wider appearance as of a halo. Fig. 12 shows a granular mucosa bordering on polypoid, with ulcers.

In each case the profile pattern should be compared with that of the striae. Thus in Fig. 13, a dysenteric case, the flattened haustra and single and twin indentations of the profile of the bowel are confirmed by an asymmetric and too closely spiked appearance of the strial pattern, shown in Fig. 14. Also in Fig. 15 the suggestion of ulceration made by the disorganized haustration is confirmed by the granular strial formation of Fig. 16.

### *Diagnosis*

The daily passage of red or reddish blood with pus and mucus is the characteristic of ulceration.

Blood in the stools must always receive attention, since serious diseases of the colon, and particularly growth and ulcerative colitis, begin insidiously. Wilks observed as long ago as 1859 that lesions of the colon were often found *post mortem* which had not been thought of during life. Many of these were secondary to long illnesses; but primary disease of the large bowel may still go unsuspected.

Out of 7,220 consecutive patients, nearly all adults, and the majority middle-aged or elderly, in all of whom the excreta were examined, frequent bloody stools were reported in 159 cases.

After examination of the patients the causes of the bleeding were diagnosed as follows:

Piles, local abrasion, fissure, fistula . . . . .	66
Ulceration of colon: ulcerative colitis 35; amoebic ulceration 13	48
Polyposis, primary . . . . .	2
Growth of colon or rectum* . . . . .	16
Cirrhosis of liver (1 also with heart disease) . . . . .	7
Lesions of stomach and duodenum (excluding post-operative haemorrhages, melaena, and occult blood, see below) . . .	6
Diverticulitis . . . . .	5
Sprue . . . . .	4
Severe anaemia, pernicious anaemia, cholaemia, oxyuris, ankylo- stoma, 1 each . . . . .	5
	<hr/> 159

\* The number of cases of growth of the large bowel was many times greater than the above figure of 16, which takes in only those in which haemorrhage was a prominent symptom.

Instances of blood in the stools in the following categories are not included in the above list:

Piles or local lesions which bled a little occasionally.

Melaena. Occult blood.

Doubtful reports at or about menstruation.

Many cases of colitis which passed occasionally a little blood. Such are of two types (i) mucous or muco-membranous colitis; (ii) colitis of varying severity but without clear evidence of ulceration.

In mucous colitis, as above mentioned, constipation with the passage of mucus is characteristic. Even when looseness or diarrhoea is complained of the rate of passage is often found to be slow, as can easily be ascertained by the use of charcoal or carmine, or by X-rays. In ulcerative colitis the rate of passage is quick.

The nature of the disease and the site of the bleeding can often be recognized by simple inspection of the dejecta. The fresh blood of piles, added to a normal stool, is different from the appearance, described above, of the faeces of ulcerative colitis; and from the mass of clear jelly, stained pink with blood, such as may arise from a growth in or above the sigmoid, passed occasionally between or with normal faeces. But in early and healing stages of ulceration of the colon great variations occur. A not uncommon error is to ascribe to piles, which may be present, the occurrence of blood which comes from farther up the bowel.

If a rectal disorder such as piles, fissure, or fistula be present an estimate must therefore be made of how far it can explain the symptoms, remembering that such a condition not infrequently accompanies chronic ulceration of the colon. A routine physical examination will as a rule determine the presence or absence of a variety of general diseases which may give rise to bloody stools, some of which are mentioned in the above analysis.

Confusion is most likely to occur with the local ulceration of growth in which constitutional symptoms may be almost absent, or of diverticulitis, situated low down and causing frequent actions; but the use of the sigmoidoscope and of X-rays will usually lead to the right diagnosis. A tuberculous tumour of the bowel does not as a rule cause symptoms which suggest chronic ulceration of the colon; the site of the lesion, though not always its nature, is detected by palpation and by X-ray examination, and there is often a local peritonitis. In tuberculous ulceration of the bowel the motions are frequent and contain pus; blood, if present, will be scanty or occult. The tubercle bacilli may be found, and there is usually evidence of tuberculosis elsewhere.

The separation of the amoebic cases from those of non-amoebic ulcerative colitis is sometimes obvious from the history and the first examination; in others prolonged and repeated searches for entamoebae and cysts may be needed.

### *Prognosis*

The *mortality* in hospital was low, 3 patients having died, 1 of whom was in the later and 1 in the last stages on admission. It is more instructive, in estimating the prognosis, to consider the total mortality of all the cases up to the present.

Of 48 patients observed in hospital in the last 19 years, 8 are dead, 7 in the ulcerative colitis, and 1 in the amoebic group.

The numbers are, of course, too small for any statistical conclusions, but an idea of the fatality in this series may be gathered by averaging the age (forty-five) and the number of years since each patient was treated (ten). If we take the ulcerative colitis group alone, which supplied most of the fatal cases, of the 35 patients 7 have died, i.e. 20 per cent. in 19 years, 6 of them of this disease, whereas in the mortality of life tables 3 deaths might be expected, or under 9 per cent.

In estimating the prognosis we must, however, take into account the effect of treatment. Of the 7 non-amoebic cases that have died 3 were hopeless on admission and 2 were not treated.

The following were the 2 untreated cases:

*Case 12* gave a three years' history of loose motions and occasional blood. He was under observation for a week. His doctor wrote that he refused all adequate treatment after returning home and was lost sight of, dying of heart disease six years later, aged 66.

*Case 24* was that of a man of 65 with ulcer of the sigmoid, who gave a fourteen years' history of the occasional passage of blood and mucus. He had become an opium addict. After a fortnight's observation he returned home, perforated later, and died after operation.

Of the 30 cases of ulcerative colitis in which adequate opportunity was given for treatment, 2 have died, Cases 5 and 20.

*Case 5.* Male, aged 66. Ten years' history, complicated by unhealed fistula and by asthma. Improved under treatment on three occasions. Died at home of large haemorrhage from bowel five months after last admission.

*Case 20.* Male, aged 52. Five months' history. Became progressively worse and died after total illness of eleven months. The disease did not yield to any measure which was tried. Caecostomy was advised and refused, mainly on religious grounds. Serum was also refused.

The mortality of those cases which were under care long enough to receive adequate treatment has been 2 out of 30, or 7 per cent. Several of these patients were severely ill in continuous or relapsing attacks for weeks at a time, with fever, rapid pulse, exhaustion, anaemia, and lethargy; and yet with continuous nursing and treatment recovered. But though well-established cases often recover with prolonged care, the advantage of early recognition and treatment of the disease is, of course, great.

A high mortality has usually been reported in cases of ulceration of the colon, up to 50 and 70 per cent. (24). Hern reports, in a series of 50 cases, a mortality of 28 per cent. in hospital and 40 per cent. with a short follow-up inquiry. In a recent valuable summary and follow-up by Hardy and Bulmer one-third were dead in an experience of twelve years. These are from the records of a general hospital with its high proportion of terminal cases, similar to the 2 cases admitted here in the last stage, and with less facility, at all events in former years, for prolonged and individual treatment.

Some writers who have analysed hospital statistics are sceptical of the value of treatment and may go so far as to suggest that the same proportion of remissions or recoveries would have occurred whatever was done. This study tends to the opposite conclusion. It appears that much better results than those of such statistics may be obtained from the continued care of cases which are received early enough to benefit. There are cases which get steadily worse, but the majority, on the one hand, respond to detailed nursing and medication, and on the other hand relapse if neglected. Some have suggested that no measure is likely to do good when the original cause of the disease is not known. This is unreasonable. The first cause of the ulceration may be dead and gone; just as, if a man's leg is broken by a motor-car, it needs to be treated as a fracture with or without a knowledge of the make or the whereabouts of the car.

*In the amoebic group of 13 cases* (average age 44.6 years, one patient had died of a different disease.

This was a woman with a four years' history on admission of passing blood and mucus. Amoebiasis had not been suspected, but was ultimately proved. The sigmoid was in a state of colitis gravis. The patient was severely ill and under treatment fourteen months. Specific remedies seemed without

effect. Recovered after caecostomy and became well and vigorous. No recurrence. Died nine years later of carcinoma uteri.

At least 5 of the cases in this group were at some time gravely ill.

The *prognosis for recovery* in treated cases, in the sense that the patient can enjoy a normal life, is shown in this series by the following figures.

Of 45 cases of chronic ulceration of the colon who received some form of treatment, from twenty years to two years ago :

	<i>Per cent.</i>
34 are well and 'carrying on' . . . . .	76
(21 of them have had no relapses . . . . .	46.7
(13 have had, and recovered from, relapses . . . . .	28.9
5 are not well but 'keeping better and about' * . . . . .	11
1 is ill . . . . .	2
5 are dead . . . . .	11

\* e.g. one, nine years later, 'fairly active socially but may have 10-16 motions a day'.

It is mentioned repeatedly in the correspondence that relapses or threatenings have followed exposure, over-exercise, a rapid enlargement of the diet, colds, influenza, and other infections. The tendency to relapse was greater in the amoebic cases, though all recovered.

As regards the *prognosis of the individual case*, patients may recover who show emaciation, great weakness, and fever. Bad signs are : a tendency to collapse, a persistently rapid pulse, anaemia of 2 million red cells or less, and a leucocytosis of 15,000 or more without a local cause that can be removed.

#### *Treatment*

Febrile and severe cases, which in hospital form the majority, were rested completely. In this series all except three of the cases of ulcerative colitis were entirely in bed for a great part of the treatment.

If a patient, even with well-established disease, has been walking about up to admission, the confinement to bed may well be made gradual. I have twice seen people become worse when suddenly put to bed altogether ; the failure of strength was probably nearing. In many more cases complete rest was followed by early betterment.

Mild and improving cases, and those with a local ulceration only, may lie and sit out of doors, and take short gentle walks in suitable weather or on sheltered paths. The return to a more normal life must always be very gradual. Some of the less severe cases, elated at a little improvement, tend to keep themselves ill by interrupting rests and treatment against the protests of relatives and friends. Clothing must be warm. Motoring usually does not suit, and any form of active exercise may bring on a relapse. Gentle hacking, for example, in convalescence, was followed by recurrence in one of these cases ; though after recovery the same patient, who was under treatment on and off for two years, has hunted and

steeped for nine years without recurrence. The patient must also be protected so far as possible against exposure to chills, disturbances, and infections. Acute relapses in a recovering bowel occurred with the common cold, influenza, thrombosis, cold weather, and pregnancy.

If people with colds, including doctors, nurses, and maids, could, especially in the early stage, be kept away from sick folk (and, indeed, from well ones) in their homes, or in hospital, the sum of illness would be lessened.

*Diet.* Formerly patients were kept on a low diet leading sometimes, with the disease, to emaciation. When it was found that most did better with a liberal supply of food, some doctors went rather far in the other direction, advocating a fairly full diet. The writer believes that he has seen harm from each of these methods. There is no rule. Careful watching and trial is needed in each case.

A few, there were eight in this series, do best on milk alone for a time, though there are some whom it does not suit. A spell on milk, after a larger diet, may do good. The appetite may be capricious and feeding difficult, and it is unwise to keep to a low or fluid diet if more variety can be taken without harm, consisting of food to which the stomach does not object and which is likely to be reduced to normal chyme by the time it has reached the caecum.

In cases with much ulceration (or with the appearance of colitis gravis in the sigmoid) and fever, the diet will be made up from milk, citrated milk, junket, cocoa, chocolate, cream soup, egg flip, jellies, thin bread and butter; with cereals to thicken the milk or as arrowroot, macaroni, and vermicelli. Eggs, fish, minced chicken, and meat are added later as in an ordinary invalid diet. When there is appetite and little or no fever, plain solid food should be given in variety and the patient's tastes followed within reasonable limits. Orange or other fruit juice or a little sieved greens or boiled lettuce should be tried cautiously as soon as possible, and if no harm follows may be continued in moderate quantity with benefit. If these cannot be taken we have supplied mixed vitamins in some other form. In patients who have been on a restricted diet for a long time the vitamin deficiency may be an important factor. In such, Vitamin B especially (23) is recommended.

Each addition of any article of food, or medicament, must be tried separately and omitted at once if there is worsening of the motions or the symptoms. Foods are sometimes asked for which do harm, especially fresh fruits, salads, or savouries and rich dishes. Plenty of fluid should always be given in the form of weak tea and other warm drinks, and, if well-borne, orange juice and soda water.

Of the 45 treated cases the diet of 29 was made up along the above lines. Details of the food taken in a typical severe case which recovered are given below on p. 571.

Other diets may be helpful in individuals. In three of the amoebic group an almost full diet, without fruit or greens, was taken from an early stage.

One patient recovered after a diet consisting mainly of macaroni paste. In another, with secondary polyposis and a moderate anaemia, liver seemed to do good. In one intractable febrile case, with a nine years' history and extensive secondary infections of mouth, nose, and eyes, after amoebic dysentery, a pure meat diet for a time, similar to that used in sprue (8), appeared to begin the improvement. The patient was led gradually on to eggs, cream, butter, jelly, and then starchy foods.

*Intestinal douching* may be of great value. Its object is to wash gently the ulcerated areas to help the removal and evacuation of decomposing discharges, and in certain cases to apply medication. Douches were used in 36 of the 45 treated cases. There are few methods the result of which depends so much upon the administrator. Gentleness in inserting the soft rubber tube, for 3 or 4 inches only, and in running in the fluid is essential. Not more than 40 oz. is used, at low pressure,  $1\frac{1}{2}$  to 2 feet, or in some cases 6 inches only. The patient then takes 6 deep breaths, lying on the left side, and then 6 on the right. If his state permits he may then take 6 more in the knee-elbow position. This procedure usually fills the large bowel, as may be seen daily in the X-ray room with the barium enema. In cases of severe colitis the first half pint usually reaches the caecum. The fluid should be helped along the colon by the breathing movements and not forced. The whole colon is thus gently washed. Douches are given on alternate days. If followed by more pain and frequency a couple of days' rest between may be needed. In a few cases they must be omitted on account of undue disturbance, but in these also it is well to make a trial again after an interval.

Normal saline was the usual fluid and was employed in 28 of these cases. If the douche is followed by griping pains these may be relieved by a good dose of belladonna, and, if more soothing is needed, a warm olive-oil or paraffin enema at night, to be retained. After a course of simple washing, a weak argyrol douche may be used once or twice a week between salines, or protargol, or tannic acid, 1 gr. to the ounce. Silver nitrate was used in 4 cases, beginning with low strengths, e.g. in one sensitive bowel 0.01 per cent., but usually 0.1 per cent. rising gradually up to 0.4 per cent. and once to 0.5 per cent. It would be given for one or two douches and then saline resumed. Some form of silver was used in 15 cases. Also used were sodium salicylate ( $7\frac{1}{2}$  gr. to a pint, alternately with saline douches), acriflavine, tannigen, albargin, thymol, peroxide, and bicarbonate of soda. A solution of potassium permanganate was much recommended a few years ago. I gave it a careful trial, but did not observe the striking results reported. Of acriflavine, 1-2,000 to 1-1,000, my experience is less. It is recommended strongly by Dr. Crohn of New York (personal communication).

Whatever douche is used, the returned fluid will be observed; also all motions, and the treatment continued or altered according to their state and to the symptoms.

When the motions become semi-solid and look normal douches are given less often, but are usually continued once a week for a time. Most convalescents can be instructed to give themselves this treatment.

*General measures and medicines.* Griping pains usually cease with the use of a hot linseed poultice. A rubber hot-water bottle will often allay milder distresses. Belladonna and hyoscyamus are also useful.

In the more acute stages, with pain and frequency, opium is invaluable. It should be prescribed with caution and covered up in medicines so far as possible; it was usually taken by the mouth, but may be put in an enema or douche. If the frequency is wearing down the patient, 15 drops of the liquid extract of opium in a mixture is given after each motion for a time. Dover's powder has been a favourite, but the ipecacuanha may cause an unpleasant and unnecessary nausea. As the bowel responds the dose needed is less and less. Opium in some form was employed in 18 of 42 treated cases in this series, that is in less than half.

Of bismuth preparations we use mostly the oxychloride or salicylate. Pure kaolin in some form, 1 dr. to  $\frac{1}{2}$  oz. or charcoal 1-2 dr., each three or four times a day in water, helps many patients, sometimes remarkably. Catechu, tannic acid, tannigen, albargin, copper sulphate, and other astringents were used occasionally.

Tenesmus may be relieved by a suppository of belladonna, with opium if necessary. If there is a rectal lesion, cocaine may be put in. Anal fomentations are soothing for inflammations of the anus and rectal canal. Cases with painful or thrombosed piles or a fissure are especially distressing owing to the frequent motions. Treatment must be directed without delay to the local inflammation.

Anaemia was treated by iron and arsenic; as the blood improves so does the patient. A mixture containing 20 drops of the tincture of perchloride of iron, with 30 drops of solution of perchloride of mercury, is recommended. I have given it to some patients who have done well.

Other medicines which we have used on occasion are sodium salicylate, calcium salts, also calcium by mouth with parathyroid hypodermically, Kerol, Dimol, Eusol, Monsol, bromide, carminatives, cod-liver oil, Radiostol, *B. acidophilus* milk, castor oil, and paraffin. Bismuth salicylate is recommended for cases complicated by the presence of lamblia (34). Hydrochloric acid may be used with benefit when it is deficient in the gastric juice.

A remedy which I have seen associated with rapid improvement is iodine. Logan reported in 1925 that he had been successful in obtaining complete remission in some cases (see also MacNaughton). Five drops of the tincture are given three times a day in a tumbler of water, increasing to 10-15 drops. Improvement in the motions, confirmed by the sigmoidoscope later, may begin within a few days. On mentioning this remedy to Dr. Bargen, he told me that he had seen similar results and that in his experience iodine was effective in about 15 per cent. of cases.

Emetine, tried in a non-amoebic case, I have seen do harm; both in man

and animals doses not far from those used in amoebic dysentery may produce in health a bloody diarrhoea. If tried, therefore, experimentally, the dose and the motions must be watched with care. Yatren, 15 gr. t.d.s., is sometimes helpful. The use of these drugs in cases of ulceration of the colon, which were originally amoebic, is discussed below.

Such measures as massage, but not to the abdomen, artificial sunlight, also diathermy, were used as called for.

Sleep must be secured. To this end the first step is the allaying of frequent motions and of pains. A bromide cachet after the evening meal is often enough in the way of sedative. If necessary it may be followed at bedtime by one containing dial ciba, medinal, or other soporific. It is well to let the cachet be of the same size and colour whatever its content. The drug can then be replaced gradually by sodium bicarbonate as improvement takes place.

Ionization with zinc (7, 31) was used in one severe case originally amoebic. Improvement in this patient seemed, however, to begin when he was put on a nearly pure meat diet, as mentioned above. In a chronic case with two visible ulcers in the sigmoid, X-ray treatment to the sigmoid area, of which a previous course had been given, was used, with saline douches. We gave 18 applications in eight weeks of 10 milliamperes for 5 minutes, with a 4 mm. aluminium filter. The ulcers healed and the disease has not recurred in the fourteen years that have since elapsed.

It was suggested by French observers that many cases of ulcerative colitis are the result of bacillary dysentery in which the primary organism is no longer in evidence, the secondary infections persisting. On this view anti-dysenteric (Flexner) vaccines were first used for recurrent cases of war dysentery. Later *antidysenteric serum* was given by Hurst (19) intravenously. In this series the chief strains of the organisms of Flexner and Shiga have been sought as a routine in cases of ulcerative colitis or colitis gravis, and the blood was tested against these organisms, but in vain; indeed, the bacilli are found in the acute stage of dysentery only, and then in but a proportion of cases of bacillary dysentery; and the agglutinins are not persistent in any sufficient concentration after the first few months. In these circumstances antisera would not seem to be indicated. A good result, however, as Hurst agrees, may be due to protein shock; and another suggestion is that the polyvalent serum may contain some substance of value from an unrecognized strain.

The practical point is the result of the trial. The recovery of the first two published sporadic cases of Hurst was remarkable, though they had not been observed long afterwards, and since then he and his colleagues have reported further brilliant results. Early cases are stated to be most amenable, as indeed they are to all forms of treatment. Doses of 40, 60, 80, and 100 c.c. of serum were given intravenously daily for the first four days, continuing with a 100 c.c. for a few days after. The reactions may be severe, but as in such cases of ulcerative colitis which do not yield to other

measures the prognosis is serious, all possible helpful means must be considered. In the newer method of giving a 10 c.c. ampoule of 5,000 units intramuscularly, the reaction is said to be less, though there is more local pain.

If the bright promise of serum treatment were fulfilled, a valuable remedy would be in our hands. It should be stated, however, that observers in England, Australia, and America have reported negative or harmful results.

In this series six patients had been treated with antidyenteric serum before admission, though all had not had such full doses as Hurst recommends. A repetition of the treatment when proposed was refused. In two of them, both severe cases, *Entamoebae histolyticae* were ultimately found. Five of the six recovered after the use of other methods of treatment and are now reported well. The sixth is still invalid, having developed phthisis. The serum was used in three other cases after admission. In another case under the writer's notice, not in this series, the good effect of antidyenteric serum, after a severe and prolonged reaction, was remarkable. The disease relapsed after a year. A similar case is reported by Gordon-Watson (14).

Hern (18), in a spirited and interesting paper, gives the impression that in his opinion other methods of treatment than that by serum are of little or no value. The danger of such an assumption is one to which the advocates of a treatment believed to be specific are exposed. They, or their followers, may be led into neglecting measures which, as the experience of this series shows, are helpful and often successful.

Bargen, on the view that the disease is caused by a Gram-positive diplococcus which he found in the bases of ulcers, uses a specific serum and vaccine, and reports good results. His views are supported strongly by some workers in the United States and Canada (25, 28). Others do not agree that the diplococcus, which is a near relation of, and some say identical with, the *Streptococcus faecalis*, is the cause of the disease (10, 13), or that specific treatment derived from it is better than other methods. In the service of Dr. Ralph Brown of Chicago<sup>4</sup> scrapings of the floors of ulcers were cultured from 75 cases according to Bargen's method, without confirmation of his results. The germ described was also obtained from cases of amoebic dysentery. The writer has had the advantage and interest of seeing and discussing a number of patients with Dr. Bargen. He said that 70-80 per cent. were improved by the serum and vaccines prepared by Dr. Rosenow. There is an occasional anaphylaxis, but it is mild—pain and constriction in the chest, or flushing, sometimes urticaria. If the patient does not respond to serum, in two or three months he receives a vaccine made from the scrapings of his ulcers. Surgical procedure was needed in about 1 per cent. only. He had tried antidyenteric serum, but had bad results. Dr. Bargen's serum was not available for the treatment of any patient in this series; and the evidence of its value must be regarded as so far not generally accepted.

<sup>4</sup> Personal communication.

*Antistreptococcic serum* had been used in two cases before admission without benefit. Good results from the serum and vaccine have been reported by Dukes and Gabriel (10).

Autogenous vaccines have been widely used in acute and chronic ulcerative colitis, made from strains of *B. coli* including the atypical coli groups of Castellani from strepto- and pneumococci (11), Barga's diplostreptococci, and other organisms. They are usually made from whatever organisms grow on ordinary media from the faeces or from an infective focus elsewhere in the body. Good results have been reported by various writers (25, 28, 10, 15).

In this series many, if not most, of the patients had been treated with long courses of vaccines without clear benefit. Incautious administration of a vaccine may, in this as in other diseases, cause severe exacerbation. A patient subject to tachycardia (p. 556 above), who may be regarded as 'allergic', showed relapse of bowel symptoms after each dose of a coli and streptococcus vaccine.

In cases of acute colitis which can be shown to be associated with, and probably due to, a particular germ, such medication offers a reasonable method of treatment, and some good results have been reported. That is not, however, so far the case in chronic ulceration of the colon.

Most of these patients recovered without the use of vaccine, serum, or operation, or, in several instances, after such measures had been tried in vain.

The following is an *example of the methods* used in a successful case:

A man of 61 (No. 4110) gave a long history of recurrent colitis for which, at the age of 38, i.e. 23 years ago, a dilated and thinned caecum and ascending colon had been resected. The present illness began four years ago, with recurrence of the passage of blood, with mucus, and diarrhoea. He had improved with holidays, but had been worse for the last three months.

On admission he was emaciated and prostrate, with fever, rapid pulse, glossitis, a distended abdomen, and 8,000–12,000 white blood cells per c.mm. There were 7 to 12 liquid motions a day, containing blood and pus. The sigmoidoscope was passed gently a few days after admission and the ulcers seen, with secondary polypi, the lining membrane between acutely inflamed. The diagnosis of further ulceration in the higher part of the colon was confirmed by X-ray, when his condition permitted, some weeks later. Treatment included complete rest and nursing in bed; medicines of bismuth and laudanum, charcoal; douches, saline, with argyrol at times. The feeding offered great difficulty at first. Abundant fluid was given in various forms, including milk and cocoa, with jellies. After a fortnight he was taking bread and butter, a little marmalade, orange juice. Fish, eggs, and chicken soufflé were then added one by one, with milk and cocoa at night. From this the patient went gradually on to plain ordinary food. Two months after admission the following is an example of a day's diet: *Breakfast*—Scrambled egg; cold fat ham; bread and butter; milk flavoured with coffee. *Luncheon*—Brains; potato cream; rice pudding with cream; toast; butter. *Tea*—Bread and butter; honey; sponge-cake; milk with a little coffee. *Evening*—Sliced chicken; potato cream; vanilla cream with added cream; toast.

At this time little red meat was given to this patient—an occasional

stewed chop—but mainly slices of chicken, cold ham, tripe, calf's head, sweetbreads, lamb's fry, fish soufflé, and similar light dishes in small quantity; followed by milk pudding, caramel cream, or apple cream. Later a little fruit was added and well borne—a ripe pear being usually preferred.

The fever subsided in a little over a week, though for another five weeks the record was occasionally just above normal at night. Blood and pus gradually became occasional in, and then absent from, the motions, which were now semiformal. The patient was not well enough to be weighed at first. Seven weeks after admission he was 7 st. 10 lb., and in the following seven weeks put on 2 stone.

After three months' treatment he began to get up a little; and in four months went home with strict directions, especially as regards daily rests and avoiding overwork. This patient reported personally,  $3\frac{1}{2}$  years later, and was well. The fact that he has recently retired from a post of great responsibility, which involved long hours, is no doubt a strong contributory factor to his continued health.

Another typical patient, a woman of 33, with a two years' history of the passage of mucus and blood, was under treatment for four months. She was becoming worse, and recurrent exacerbations of symptoms, with anaemia, a raised temperature, and a pulse of 88–124, usually over 100, gave rise to anxiety. In such cases any disturbing measure, such as an intestinal douche, needs to be omitted at times. A reasonable persistence in treatment, however, led to recovery, and the bowel lesions were no longer to be seen. Tannigen was used as well as argyrol, and iron and arsenic for the anaemia. In this case also, as in most severe cases, the feeding required close attention. A year later she was taking one intestinal douche a week, was well, and had put on a stone since discharge. A recurrence, much milder, followed and yielded to treatment. This patient has been seen recently, six years later, and is well. There is occasional looseness if overwrought.

The *length of treatment* in hospital varied from two weeks to six months, the average period being fourteen weeks for all the cases, also for each group separately. The total period of treatment was, of course, longer, since the régime advised was in most, if not all, cases continued afterwards at home under close medical care.

The *after-treatment* in these cases is of great importance. A regular life, a rest in the middle of the day, early hours, plain diet, warm clothes, and the avoidance of physical and mental strain should be continued indefinitely. A teaspoonful of paraffin morning and evening is generally advised. Stress has already been laid on the well-known liability of the disease to recur; but it is clear that relapses have followed avoidable indiscretions.

*Treatment in amoebic cases.* It has already been stated that this group of 13 patients does not comprise cases of amoebic dysentery as such, but only those which fall clinically under the heading of chronic ulceration of the colon. In several the association with amoebiasis had not been known, and, as mentioned above, was discovered after admission. The length of history of the symptoms of ulceration of the colon in five such unsuspected cases was, in years, 9, 4,  $1\frac{1}{2}$ , 1 and  $\frac{1}{4}$  respectively.

The general treatment is the same as that for ulcerative colitis. Those known to have had dysentery had received specific treatment before admission,

some of them many times; the aim in these was to attack the entamoeba afresh, by varied methods, and at the same time to influence so far as possible the chronic ulceration, in which secondary infection plays a large part.

In a recent discussion the modern methods of treating intestinal amoebiasis have been fully reviewed (27). Here remarks will be made only upon our experience in these resistant cases.

Emetine hydrochloride was usually injected under the skin as a first step, beginning in doses of  $\frac{1}{2}$  to 1 gr. daily for 10 days, varying according to the tendency to nausea and vomiting. If well borne, up to 1 gr. may be given at a time, but not more than 15 gr. in a course. After an interval emetine bismuth iodide, 1 gr., or, latterly, periodide, was given by the mouth, in a gelatine capsule on an empty stomach at night; if nausea and vomiting became severe they were omitted, the course of emetine hydrochloride hypodermically being repeated later. Auremetine, which seldom causes vomiting, we have in recent years found useful, in doses of 1 gr. in gelatine capsules three times a day on alternate days.

Relief of bowel disturbance after a course of emetine is sometimes obtained by a mild dose of castor oil followed by two days of rather less food.

In a severe and resistant case I used in 1919 *emetine by the bowel* in a dose of 1 gr. to a pint of normal saline, and this measure appears to be of value.

For example, a man of 65, with a three years' history, had had repeated courses of emetine under the care of experienced physicians and seemed worse after each. Emetine poisoning can, indeed, occur with doses which do not, in that patient, destroy the amoeba (27). The administration for 16 consecutive days of the emetine douche seemed to be associated with a definite improvement. It was followed by other measures, e.g. douches of 1-6,000 thymol, a course of periodide, totalling 90 gr., Novarsenobillon, and later two further courses of periodide. Recovery took place. Four years later this patient reported that he was well, and that any tendency to recurrence was allayed by the use of a similar emetine douche or more periodide.

A recent writer (27) reports that emetine douches have been followed by severe abdominal pain, tenesmus, and diarrhoea. A strength, however, of 4 gr. to 10 oz. was used by him, i.e. 8 times the strength recommended above. My object in giving 1 gr. in a douche was to put into the large bowel the maximum dose usually given daily under the skin.

Yatren was used as well as emetine hydrochloride in later cases, both by mouth (two cachets of  $7\frac{1}{2}$  gr. daily) and bowel (8 oz. of 2½ per cent. solution) to be retained, after a wash-out of 2 per cent. sodium bicarbonate. The treatment is continued up to 10 days. One patient was worse after it and the course was therefore interrupted. The British-made Quinoxyl is reported to be equally useful. Manson-Bahr (27) recommends an after-treatment of two pills of 4 gr. of Yatren or Quinoxyl at night for three weeks.

Each method must be followed carefully and consistently, and, if unsuccessful, another method tried. For example, in this group recovery in one

case followed emetine, in another douching, and a third Yatren. All these were long relapsing cases, and are still well 9, 13, and 17 years after respectively.

Stovarsol we have found of much help in the later treatment of resistant cases.

For example, in a refractory recurrence the treatment which proved successful was as follows. *First day*: one tablet Stovarsol in 1 oz. water. *Second day*: two doses. *Third and fourth days*: three and four doses respectively. *Fifth day*: auremetine, 1 gr. three times a day. *Sixth day*: four doses of Stovarsol as on fourth day. *Seventh and succeeding days*: auremetine three times a day on alternate days with Stovarsol, four doses. In this case a total of 117 grains Stovarsol and 18 gr. auremetine was given.

No rash was noted from the use of Stovarsol.

All forms of treatment are checked by repeated examinations of stools for the *Entamoeba histolytica*.

For after-treatment two Stovarsol tablets may be given on two days a week for three weeks out of each month. The faeces are examined at least once a month after leaving; and a week of daily observation in hospital is advised after six months.

### *Surgery*

Local rectal conditions should be dealt with, but a diagnosis should be made first of the state of the bowel above. The removal of simple piles, for example, may lead to disappointment if the fact that blood is coming from higher up the bowel has not been ascertained.

Three patients had undergone a partial colectomy before admission. Two of them had been well for several years, and did well again on medical treatment after recurrence. Another had not benefited. She was a frail person, the subject of colitis gravis affecting other parts of the bowel as well as that removed. Under medical treatment, first in hospital and then at home, she improved steadily, and her doctor reports now (seven years later) that she is living a normal life.

Caecostomy had been done before admission in one case in this series. It had led to much good, but the ulcers were unhealed, and the opening had been allowed to close. The patient recovered with douching and other treatment and remains well.

The writer's experience of surgery is derived mainly from cases not in this series. In ordinary ulcerative cases which do not respond to the treatment described in the foregoing pages, and especially when skilled intestinal douching is not available or is badly borne, irrigation from the caecum is advisable. In such appendicostomy (20, 24) or caecostomy must always be considered without undue delay. The mortality is likely to be high if it is left too late (17). A small opening may be made with a soft catheter purse-stringed into the caecum, as recommended by Thorlakson (33). Ileostomy is

used latterly by some surgeons, and is sometimes done under spinal anaesthesia. Klose (22) prefers the caecal anus in order to rest the colon entirely. Such operations are, as Thorlakson says, a means to facilitate more thorough medical treatment, and it is probable that they should be done, in resistant cases, more often.

Caecostomy was advised in two of these cases. One of them, Case 20 (see p. 564) declined any operation or serum, on religious grounds, and ultimately died. My impression was that caecostomy would have been of benefit, especially as, owing to rectal lesion, he was intolerant of intestinal douching. The second case, originally amoebic, had resisted specific and general treatment for a year. Antidysenteric serum had been given before admission. Caecostomy was then done, and led to complete recovery. The opening should not be allowed to close until the motions are free from blood and pus and the sigmoidoscope shows that the lining of the bowel is healthy. In a third case in the series, in which symptoms disappeared under the first course of treatment, caecostomy was done on recurrence, now 10 years ago. This patient is well and active. She refuses to have the opening closed, washing through the colon by its means once a day.

The other five cases which have proved fatal were not suitable for operation, either because they made good progress while in hospital, or because of the complications, or because the patient was *in extremis* on admission. Several of the cases that recovered without operation were as severe as any uncomplicated cases I have seen.

Severe stricture was not found in this series. It is uncommon, since the ulceration is usually shallow, but it must be thought of in persistent cases and looked for with X-rays. Operation may be (24, 14, 19) needed. I saw a boy in a Chicago hospital, under the care of Dr. Ralph Brown, whose colon had been washed through an ileostomy opening for ulcerative colitis for fifteen years. A purulent discharge continued. The lower bowel was so constricted that barium, introduced for X-ray observation, could be seen only in places.

### *Summary*

The paper is founded on the writer's clinical experience of chronic ulceration of the colon, with special reference to 48 consecutive cases investigated and observed in detail. In 13 of the cases chronic ulceration was associated with amoebiasis. Several of these had been treated for months or years without knowledge of that fact.

Catarrhal colitis is described as of two types: (a) chronic mucous or mucomembranous colitis; (b) infective catarrhal colitis. The (b) type may go on to ulceration, (a) usually does not. Colitis gravis is defined as a severe general inflammation of the mucous membrane of the colon, with or without ulceration visible to the sigmoidoscope or demonstrable on X-ray films.

The average age of patients with ulcerative colitis is in the forties. The disease usually occurred in those who were or had been unhealthy from some

other cause. Fourteen of the patients with ulcerative colitis had also some rectal disorder. In half of these the rectal disease had preceded the ulcerative colitis, and in half it had not.

An analysis of symptoms and signs is given with the results of examination of stools, blood, and of the bowel with the sigmoidoscope.

In 7,220 consecutive patients admitted, frequent bloody stools were reported in 159. In 66 the bleeding came from rectal or anal lesions, in 48 from chronic ulceration of the bowel, and in the remainder from growths, cirrhosis, and other diseases.

The X-ray appearances of the ulcerated bowel are detailed, with special reference to the direct signs of ulceration seen in stria patterns.

An account is given of the various methods of treatment found useful in a series of cases; and details of the medicinal measures and the diet in some severe cases which recovered. Whenever possible the patient was well fed. Vaccines and sera, which were used in a number of cases, are discussed, the conclusion being reached that their value is at present uncertain.

The special measures found useful in treating resistant cases of amoebiasis with chronic ulceration are described.

Inflamed piles, fissures, &c., must be treated surgically. Appendicostomy, or caecostomy, in the course of medical treatment is seldom needed, but may be a valuable aid, especially if intestinal douching is ill borne.

With adequate medical treatment the prognosis and the mortality are less grave than some recent authors have asserted.

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## DESCRIPTION OF PLATES 25 to 32

FIG. 1. Shows flattened haustration on the affected side bordering on inhibition. A deep indentation with a sharp septum can also be seen, a spasmodic phenomenon associated with an ulcer near by in the same haustrum. Indirect sign.

FIG. 2. A jagged transverse colon typical of advanced disease. There are numerous crater-shaped projections throughout the bowel, which dilated well. Direct signs.

FIG. 3. Direct signs of ulceration. Two raised parts can be seen with a slight depression between, as of a tray in profile (see arrows). The sigmoid has been shortened in the course of the disease: the lumen is also narrower than it was five years earlier.

FIG. 4. Three craters in profile in a bowel with rigid walls. Views at other angles show more such craters.

FIGS. 5 and 6. Strial patterns of the transverse and descending parts of a normal colon.

FIG. 7. Three variously shaped craters in the transverse colon, in transillumination.

FIG. 8 shows inhibition, a few craters in the descending colon, and unduly long striae.

FIG. 9, from the same case, shows abnormally long striae characteristic of severe colitis, usually ulcerative.

FIGS. 10 and 11 show the honeycomb appearance and scalloped outline of ulceration with polyposis.

FIG. 12, from another polypoid case, shows scalloping in the transverse colon in profile, and ulcers in the strial pattern of the descending and iliac colon. Note also the fluffy outline of the strial pattern.

FIG. 13. The colon shows flattened haustra and single and twin indentations, associated with dysentery.

FIG. 14. The strial picture of the same case. It is not far from normal, but the striae are too closely and sharply spiked at the involved parts, particularly the upper and lower borders near the spine.

FIG. 15. The profile picture shows the indirect sign of broad impressions and asymmetric haustration.

FIG. 16. The strial pattern of the same bowel. It shows a granular formation, which is regarded as evidence of inflammation of the mucosa.

FIG. 17 shows three photographs of a barium enema at different stages of emptying, in a case of advanced ulcerative colitis.

FIG. 18. From two cases of ulcerative colitis showing some polyposis.

1



2



3



4



FIGS. 1-4



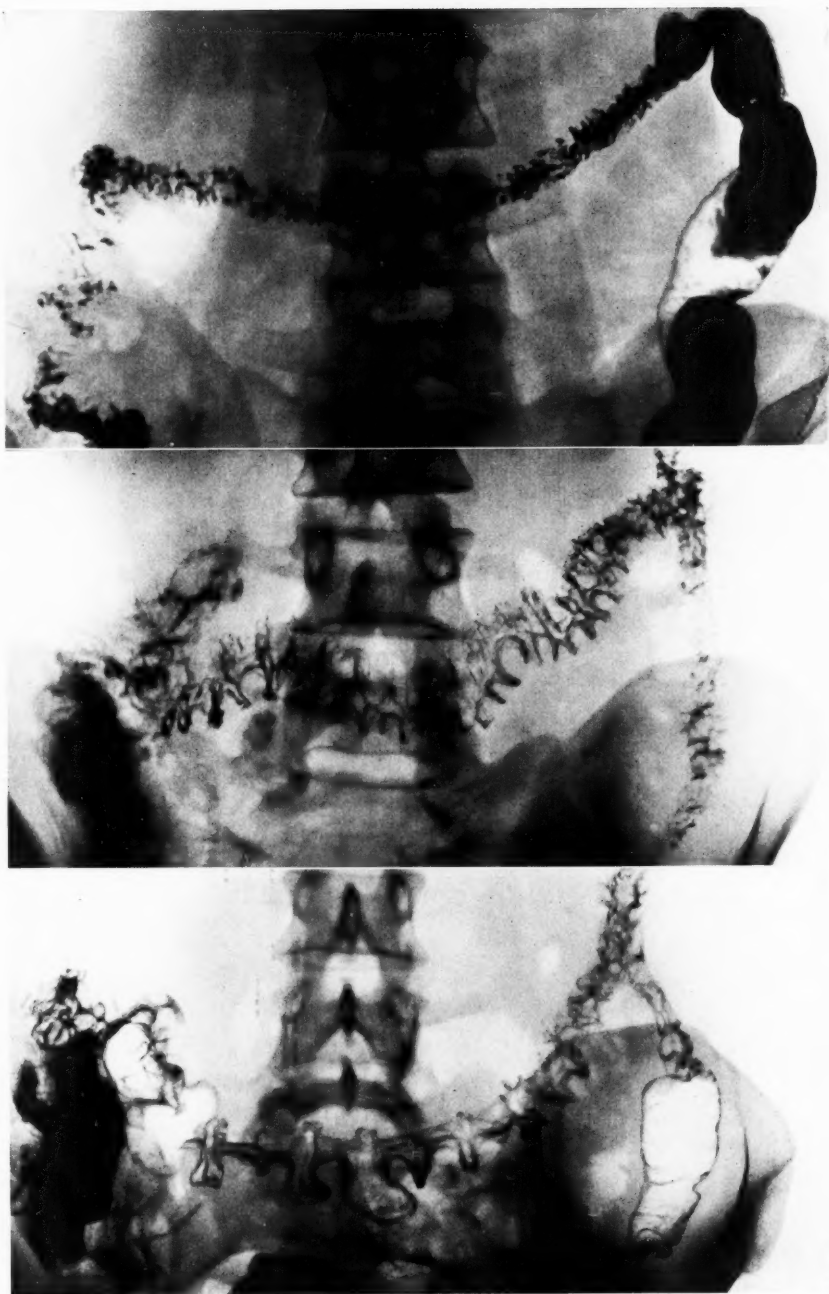


FIG. 5



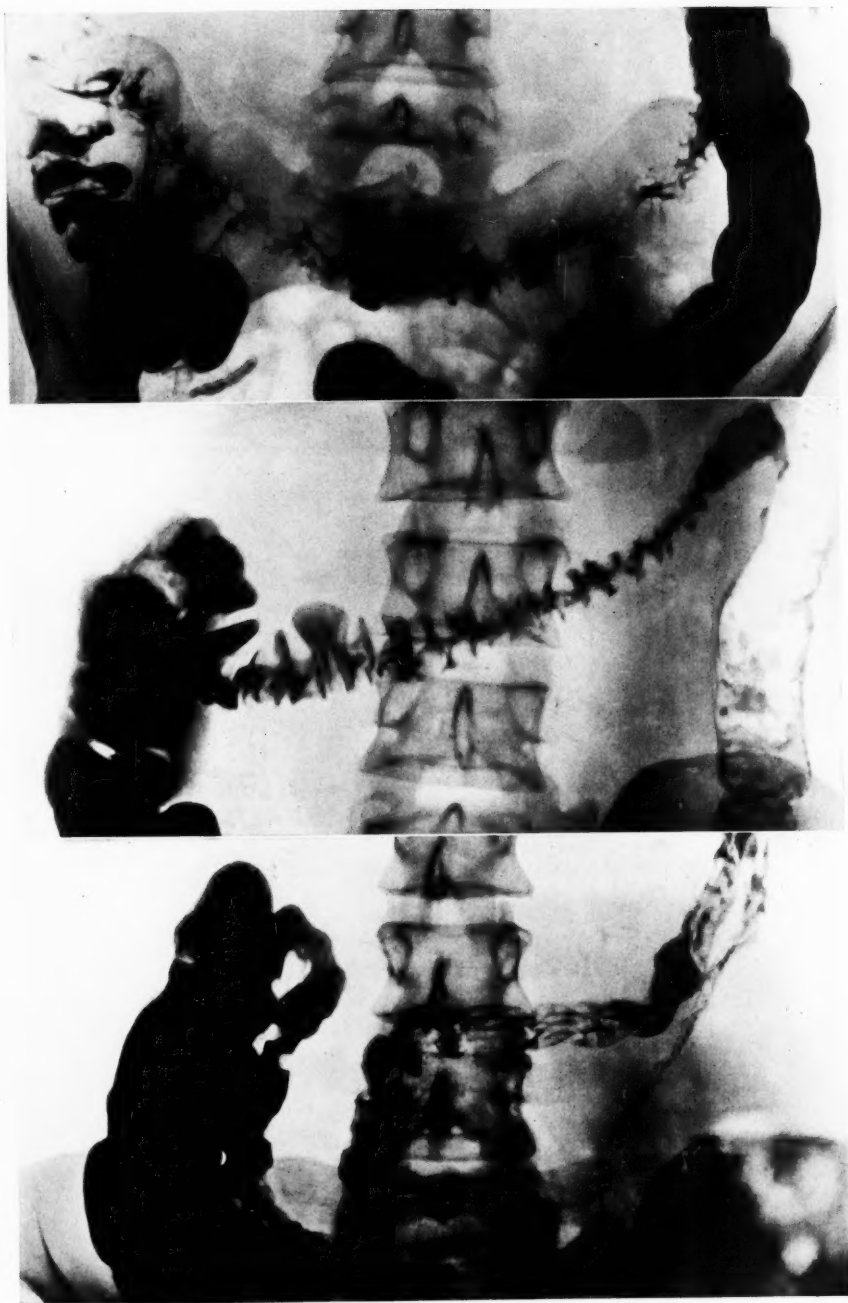


FIG. 6





FIG. 9

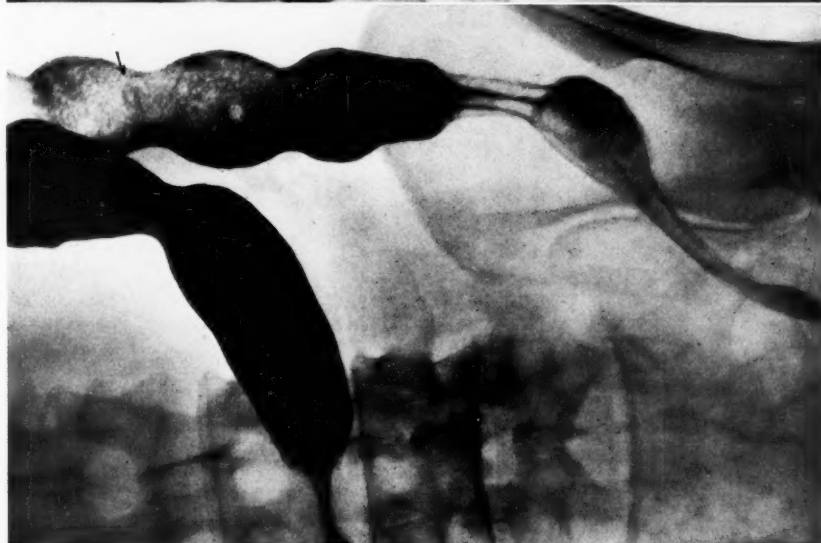


FIG. 8



FIG. 7

Ulcerative colitis. Smooth mucosa with direct evidence of ulceration. Arrows indicate ulcers





FIG. 12



FIG. 11

Granular mucosa (polypoid). Mixed type. The arrows indicate ulcers



FIG. 10



13



14



15



16

FIGS. 13-16



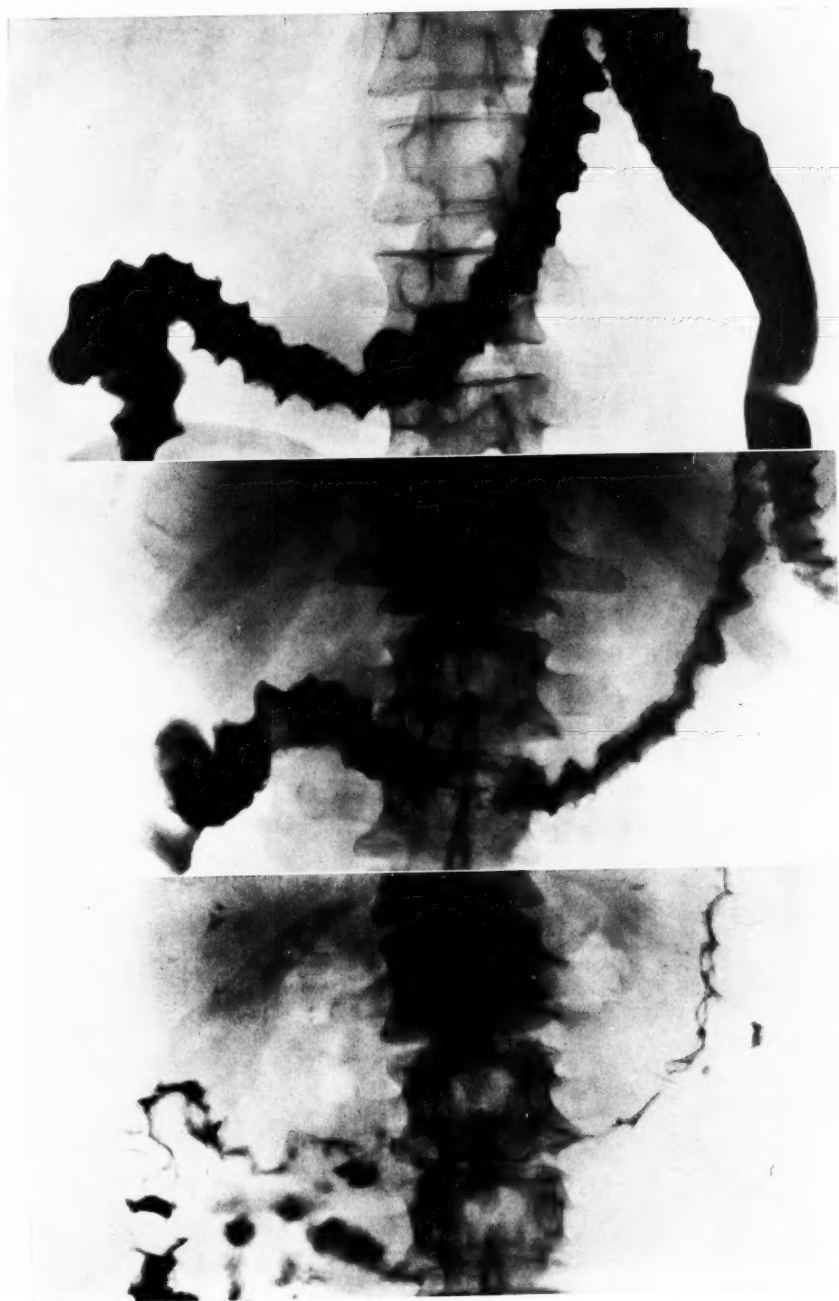
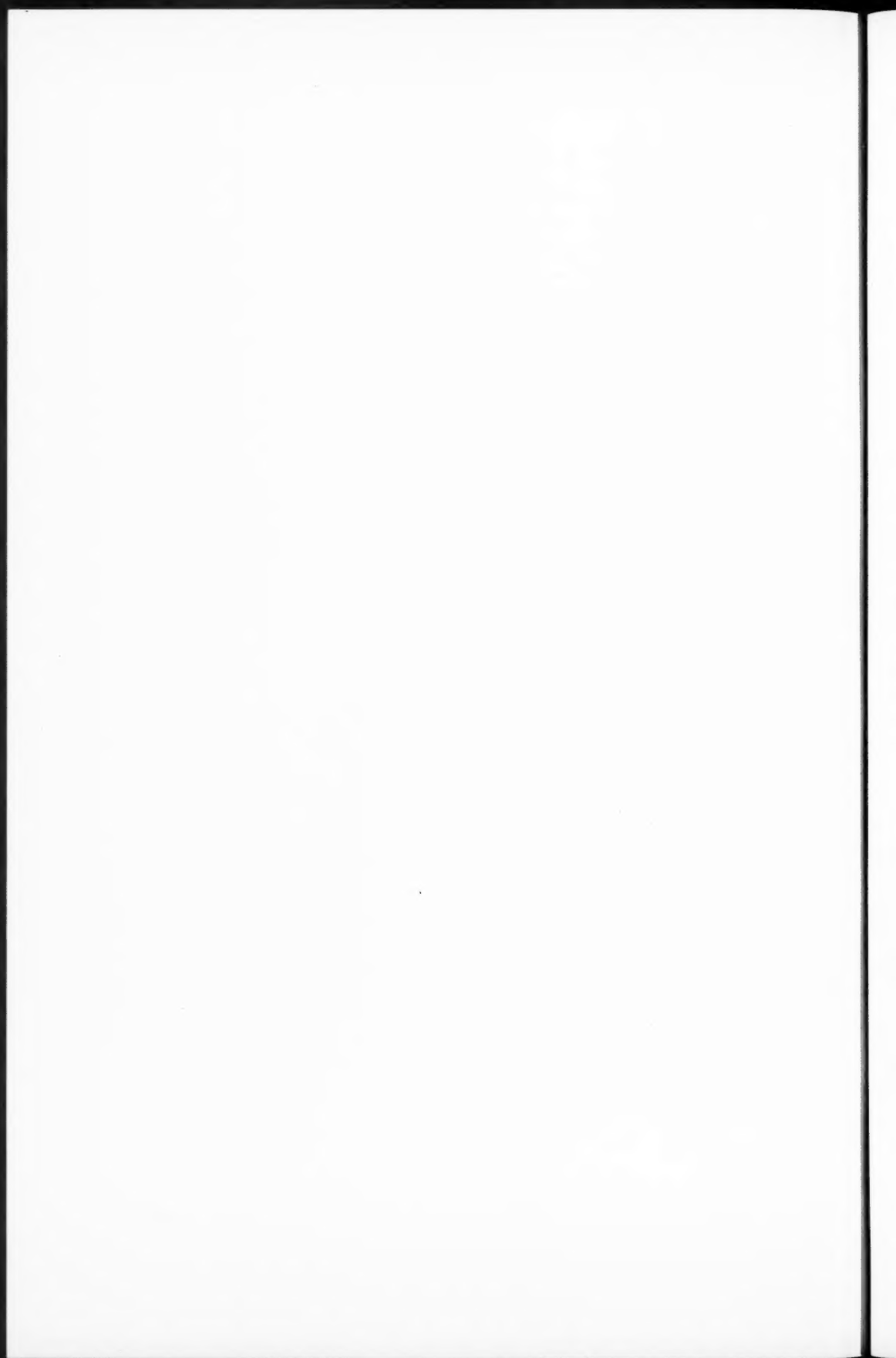


FIG. 17





FIG 18



OXYCEPHALY<sup>1</sup>

## WITH A REPORT OF THREE CASES IN ONE FAMILY

By ERIC SKIPPER

(From the London Hospital)

With Plates 33 and 34

OXYCEPHALY (synonyms: acrocephaly, turmschädel, tête à la thersite, &c.) was recognized by the ancients. Oribasius was familiar with it (1), and both Hippocrates and Galen were aware of malformations of the skull which they sought to bring into causative relationship with the condition of the cranial sutures (2). In modern times interest in oxycephaly dates from Virchow (3) who stressed the aetiological importance of early closure of the cranial sutures, and from von Graefe (4) who first definitely described the concomitant visual defect.

During the last three years the writer has had under observation a mother and two children suffering from oxycephaly who exhibited certain unusual features; one of them was subjected to cranial decompression. From a survey of the literature it is obvious that the surgical treatment of oxycephaly has seldom been attempted.

*Case I. Mrs. D. F., born April 1902.*

*History.* In early youth she suffered from headaches of moderate severity. Her eyes had always been prominent, but she had never noticed anything wrong with her vision, and she was unaware that her head was abnormally shaped. Her first two children, subsequently shown to be oxycephalic, were born early in 1926 and 1927 respectively. In the latter part of 1927 she had a four months' abortion, and shortly afterwards her appendix, left ovary, and an ovarian cyst were removed. In 1928 a fourth pregnancy terminated prematurely in a still-born child, the head of which was not apparently deformed. Another child, which is normal, was born in 1930. Her husband and her mother have been examined and exhibit no oxycephalic characteristics, and it is said that none of her other relatives are deformed in any way.

*On examination* she was an intelligent, well-developed woman. Height 5 ft. 2½ in. On cursory examination the head seemed normal, but closer inspection revealed that the skull was unusually dome-shaped and rose to a keel-like elevation situated along the sagittal suture in the region of the bregma. This *crista sagittalis* was hidden from view by the hair. The forehead and lower jaw were receding, making the nose and upper jaw appear prominent in profile. The skin of the face was coarse and bore numerous

<sup>1</sup> Received June 13, 1934.

small warts. Measurements of head: <sup>2</sup> horizontal circumference 52.5 cm.; height 12.25 cm.; maximum length 17.5 cm.; maximum breadth 13.5 cm.; cephalic index (maximum breadth ÷ maximum length × 100) 77.1. The superciliary ridges and frontal sinuses were small. The nose was asymmetrical, the nasal septum deviated to the left, and the palatal arch was high and narrow. Many of the teeth were carious, but they were not crowded. The eyes were prominent, abnormally far apart, and the outer canthi were lower than the inner. The left eye exhibited a divergent squint (Fig. 1). The conjugate ocular movements were full in all directions and there was no nystagmus. There was bilateral ptosis, more marked on the left side. The pupillary reactions were normal. Vision: right 6/12; left 6/9; visual fields full. Ophthalmoscopy revealed mild bilateral optic atrophy of the 'secondary' type, both disks being pale with blurred edges. The retinal vessels were small. The senses of hearing, taste, and smell were unimpaired, and there were no other abnormal physical signs in the nervous system. Wassermann reaction negative. X-rays of the skull revealed the peaking of the apex and moderate convolutional thinning (Fig. 2). The corticalis was especially thin at the vertex and in the temporal regions. No suture lines were visible. The *sella turcica* was large and deep.

When last examined (1933) the patient was well and her condition was unchanged.

*Case II.* Audrey F., born January 1926, the eldest child of Mrs. D. F., was admitted to hospital under the care of Dr. Riddoch on November 1st, 1930, complaining of failing eyesight.

*History.* No abnormality of the head was noticed at birth. Labour was difficult and was assisted by forceps. She walked at twelve months and talked at fourteen months, and, apart from chicken-pox and measles, had had no previous illnesses. Early in 1929 the mother noticed that the child's left eye tended to turn outwards. Spectacles were prescribed, but did not correct the squint. In August 1930 she began to drop toys without being able to find them again, and would walk into obstacles as if they were not perceived. During September it was observed that her eyes were prominent. Vision rapidly failed until the child could only distinguish between light and darkness. She sometimes saw 'pretty coloured specks' in front of her eyes. There was no history of fits or headaches. A tentative diagnosis of hydrocephalus following meningitis had been made elsewhere.

*On examination.* A well-developed, rather precocious child, with a curiously deep voice. Height 42 in., weight 2 st. 9 lb. The vertex of the skull was dome-shaped and rose to a *crista sagittalis* which was less pronounced than that of Case I, and which was visible only after the head had been shaved (Fig. 3). There was bulging of the parietal regions and of the temporal fossae. Measurements of head: horizontal circumference 48.4 cm.; height 12 cm.; maximum length 16.5 cm.; maximum breadth 13.1 cm.; cephalic index 79.4. The superciliary ridges were absent and the frontal sinuses small. The nasal septum was deflected to the right, but there was no nasal obstruction. A small dilated vein was visible on the bridge of the nose. The palatal arch was very high but not narrowed, and there was no crowding of the teeth.

<sup>2</sup> The measurements were taken by the methods described in 'International Agreements for the Unification (a) of Craniometric and Cephalometric measurements, (b) of Anthropometric measurements to be made on the living subject'. W. L. H. Duckworth, Cambridge University Press, 1913. The head-spanner used was kindly supplied by Professor H. A. Harris.

The tonsils were moderately enlarged. There was moderate bilateral exophthalmos with ptosis, an external squint of the left eye, and coarse irregular nystagmus in all directions. Considering the state of vision, conjugate ocular movements were good, but there was no convergence. The pupils, equal in size and moderately dilated, showed hippus and a good but delayed reaction to light. Little vision remained, the child being just able to perceive light from an ordinary household electric bulb held close to the eyes. Ophthalmoscopy, which was difficult, revealed advanced optic atrophy, both disks being small, dead white, and flattened with slightly blurred edges. The laminae cribrosae were not seen. The retinal vessels were small. The sense of hearing was good. No tendon reflexes were obtained in the upper limbs, the left knee-jerk was brisker than the right, both ankle-jerks were absent, and the plantar responses extensor. The abdominal reflexes were brisk and equal. The heart, lungs, and abdomen were clear, and the Wassermann reaction negative. Radiography of the skull showed a pronounced beaten silver appearance (Fig. 4). The cortex was thin, especially at the apex of the skull and laterally where the tables could not be distinguished. The pituitary fossa was large. Careful search of stereoscopic films revealed no suture lines. In the antero-posterior view the *crista sagittalis* and the lateral bulging were evident.

*Treatment.* In spite of the severe degree of optic atrophy it was considered just possible that some improvement of vision could be effected by means of a cranial decompression, and the child was transferred to the care of Mr. Cairns who operated on November 25th, 1930. Under intratracheal gas and oxygen anaesthesia the right ventricle was tapped through the parietal bone and was reached at a depth of 5.5 cm. The intracranial pressure was high, for the cerebrospinal fluid rose to a height of 440 mm. in the manometer. Only about 4 c.c. of fluid could be obtained, suggesting that the ventricle was small. (Six lymphocytes per c.mm., protein 0.015 per cent., Wassermann reaction negative.) A bilateral subtemporal decompression was then performed. The portions of bone removed were very thin, and showed prominent convolutional markings on their inner surfaces. On incising the dura, which was also thin, the brain bulged considerably. She recovered rapidly from the operation, and was well and cheerful two days later. The wounds healed normally; there was considerable bulging of the decompressions. The child left hospital on December 20th.

*Progress.* A few days later there was pain in the left ear, followed by a purulent discharge which lasted one week. At about this time attacks of generalized headache accompanied by vomiting commenced. These recurred about every ten days, and between them the child apparently felt quite well. Re-examination in April 1931 revealed no change in her condition, save that the exophthalmos was definitely less marked. Unfortunately there was no evidence of returning vision. Light perception still persisted. When last seen (June 1933) the child was recovering from vaccination, but was otherwise well. She was bright and alert, and seemed normal mentally. There had been no headaches for four months. The hernia cerebri were still tense, but the eyes had receded farther and the *crista sagittalis* was less prominent. The state of vision and the appearance of the optic disks were unaltered. Both plantar responses were flexor.

*Case III. Reggie F., born February 1927, the second child of Mrs. D. F.*

*History.* His birth was normal. He was rather slow in learning to talk, but walked at seventeen months. Except for nocturnal enuresis during the

last two years, he had always been quite well, and his mother had never noticed anything unusual in his appearance. There was no history of fits, headaches, or visual impairment.

*On examination, December 1930.* A healthy-looking, intelligent boy, height 39 in. The general shape of the head was normal save for a minor degree of brachycephaly and some fullness laterally. A low *crista sagittalis* was palpable. Measurements of head: horizontal circumference 50.5 cm.; height 11.2 cm.; maximum length 16 cm.; maximum breadth 13.5 cm.; cephalic index 84.4. The supraciliary ridges were poorly marked. Nasal respiration was difficult, and the child was a mouth breather (Fig. 5). The nasal septum was deflected to the right. Both tonsils were large. The palate was high and narrow, and many of the teeth were carious, but there was no crowding. Vision was apparently normal. There was a mild degree of secondary optic atrophy, both disks being pale pink and slightly swollen with indistinct edges. The retinal vessels were rather small. There was very slight bilateral exophthalmos with ptosis. The remainder of the nervous system, the heart, lungs, and abdomen revealed nothing abnormal on examination, except a shallow Harrison's sulcus. Slight *genu valgum* was also present. Radiology of the skull (Fig. 6) revealed the tendency to peaking, and extensive convolutional atrophy. The corticalis was extremely thin, especially laterally. As in the other cases, no sutures were visible. The pituitary fossa was normal in size and shape.

*Progress.* As vision was good, it was decided not to operate unless optic atrophy progressed. The child was therefore allowed to remain under medical supervision at home, the mother being instructed to keep a careful watch for signs of visual failure. When last examined (June 1933) the optic atrophy had not advanced, and eyesight was apparently normal. As the boy is now 6 years of age it is probable that the optic atrophy will remain quiescent (*vide infra*).

Radiograms of the limbs of the above cases disclosed no abnormality.

#### General Discussion

Oxycephaly is a rare anomaly. It essentially affects infants and young children, and, in its typical severe form, is usually evident at birth. Greig (5), however, described a delayed type in which the deformity is milder and becomes apparent after the first few years of life. Occasionally oxycephaly is transmitted from a parent to one or more children. Transmission to the third generation is rare, but has been noted (6, 7). There is probably no difference in the sex incidence, Günther (8) suggesting that the alleged preponderance in males is due to a tendency of the coiffure in the female to cloak the deformity. He also states that oxycephaly is more common in twin than in single pregnancies.

It is now generally believed that the anatomical peculiarities of oxycephaly are produced by a combination of two factors: premature closure of the cranial sutures, and pressure exerted by the growing brain upon a relatively unyielding skull. The human brain grows rapidly during infancy and childhood, increasing in weight about 85 per cent. during the first six months of post-natal life (9), and attaining 90 per cent. of its complete development by the fifth year (10). The accommodation of the growing brain by the cranium

is rendered possible by its sutures which do not disappear until after the brain has reached its greatest size. Synostosis between the skull bones normally commences at about 30 years of age on the entocranial aspect of the lower half of the coronal suture. Over 60 years of age all sutures are obliterated internally (11). Park and Powers (12) have produced strong evidence to show that the coronal suture is the first to join in oxycephaly, and that it is usually partly or completely fused in the new-born oxycephalic. Hence, as Virchow pointed out, growth of the skull is necessarily limited in an antero-posterior direction. During infancy there is therefore a compensatory accession of growth in other directions, particularly in the vertical, producing the typical 'tower-shaped' head of oxycephaly. Moreover, during the first year or two of life the other sutures join, so that the skull, including its facial portion, becomes sutureless. This sutureless condition is invariable in true oxycephaly, and serves to distinguish it from deformities due to irregular synostoses, named 'pseudo-oxycephaly' by Greig. In the delayed type of oxycephaly, synostosis probably begins at some period after birth. The premature generalized synostosis must be considered developmental in origin (5, 12). The not rare concurrence of the anomaly in a parent, and the occasional coexistence in an oxycephalic of other developmental defects, such as deformities of the limbs, congenital morbus cordis, or acholuric jaundice, lend colour to this contention.

The cardinal symptoms of oxycephaly are defective vision and headache. As pointed out by Morley Fletcher (13) in his valuable paper, the former is almost invariable, and is most commonly first noticed during the first five years of life. It varies from slight impairment to complete blindness, and is due to optic atrophy following papilloedema. Papilloedema has been observed, but has usually given place to atrophy before the patient is brought for medical examination. Atrophy progresses to a certain extent in childhood and then remains stationary, never leading to blindness in adult life. Although its cause is still not absolutely certain, there is much to suggest that it results from increased intracranial pressure. Evidence of high intracranial pressure in oxycephaly is seen in the convolutional atrophy of the skull bones, and in the bulging of the brain on incising the dura at operation. In Case II, moreover, the intraventricular pressure was directly measured and was much above normal. Behr (14) in thirteen oxycephalics found the pressure of the cerebrospinal fluid raised at lumbar puncture. The suggestion that atrophy is caused by constriction of the nerve within the optic foramen, either from a bony narrowing of the latter or from an abnormally placed carotid artery, has not been generally confirmed (5, 15, 16, 17). As possible contributory causes may be mentioned stretching of the optic nerves from upward displacement of the brain during the vertical expansion of the skull, and stasis in the retinal vessels consequent upon defective return of venous blood from the head. Thus Greig has shown that the jugular foramina may be very small, and the circulation in the jugular veins negligible. Intelligence is generally normal, but may be impaired, poor vision undoubtedly

contributing to this in many instances. The oxycephalic is usually a mouth breather from deflection of the nasal septum and deformity of the posterior nares. Anosmia is frequent. Uncommon symptoms are convulsions, deafness, and loss of the sense of taste.

The cases reported in this paper are remarkable for the extremely mild degree of cranial deformity, and the writer has found no record of any instances of oxycephaly in which the departure from the normal configuration of the skull was so slight. Usually the oxycephalic head is too high, short, and broad, the first characteristic being the most striking. The brachycephaly is considerable, about 70 per cent. of oxycephalics having a cephalic index of over 86 (8) (Mesocephalic = 75-80). The forehead rises steeply to a rounded or peaked vertex, the acme of the deformity being in the region of the bregma, while the occiput is flattened and the skull bulges laterally. In these patients, which are evidently examples of delayed oxycephaly, the general shape of the head is almost normal, and only Case III is brachycephalic. Yet the cases are in all other respects typical examples of oxycephaly, and the diagnosis cannot be doubted. The crested vertex, deflected nasal septum, palatal deformity, and the condition of the eyes of each patient are particularly characteristic. Finally the X-rays of the skull revealing convolutional atrophy and no trace of sutures are, in conjunction with the clinical signs, diagnostic.

#### *Treatment*

The chief object of treatment is the prevention or the arrest of damage to vision. Of the various methods that have been employed to effect this, two, namely, cranial decompression and resection of the roof of the optic canal, require discussion. The writer has collected details of seven cases upon which the former operation was performed (15, 18, 19, 20). Of these, one died three hours after decompression from dural haemorrhage. Three patients had advanced optic atrophy. In two of these vision improved slightly; the third, who was already blind, was lost trace of after operation. The best results are reported by Hildebrand (19) and by Sharpe (20). Hildebrand's case, aged 3 years, showed early optic atrophy, but the optic disks are said to have become normal in appearance two years after a right cerebellar decompression. No reference is made to visual acuity, which was presumably good, but it is stated that the proptosis diminished. In one of Sharpe's cases, aged 9 years, with alleged mild bilateral optic atrophy, vision had been blurred at times, although it was practically normal when tested. A bilateral subtemporal decompression was carried out at two sittings, and all haziness disappeared from the optic disks after the second operation. In another patient of Sharpe's, 10 years old, who also had a mild degree of optic atrophy with blurred vision, a right subtemporal decompression was performed. One year later vision was normal, but details are inadequate, and there is no note of the condition of the fundi subsequent to operation.

It should be mentioned that in all the above cases there were indications of a high intracranial pressure at operation.

Schloffer (21), who believed with Behr that optic atrophy resulted from pressure exerted by the carotid artery upon the nerve at its foramen, devised a transfrontal operation for removal of the roof of the optic canal. His technique was later modified by Hildebrand who approached the canal through the orbit. Unfortunately it is not possible strictly to compare the results of this procedure with those of decompression, for, of six cases subjected to it (19, 21, 22), in five optic atrophy was advanced. An insignificant improvement of vision occurred in two of these. In the sixth case, cited by Hildebrand, although eyesight was not benefited, it is said that the optic atrophy, previously regarded as progressive, was arrested.

More experience in the treatment of oxycephaly is necessary before definite conclusions can be drawn. But, in the present state of knowledge, decompression would seem a more rational undertaking than the difficult operations upon the optic canal devised to remove a very hypothetical source of local pressure from the optic nerve. For real success it is essential that decompression be carried out when optic atrophy is still in an early stage or when papilloedema only is present. Many cases require no treatment, for, although normal vision is rare, the optic atrophy may remain of slight extent. In most oxycephalics, if the optic atrophy progresses, it does so during the first few years of life, for it is then that the brain is growing most rapidly. The importance of an early diagnosis is thus manifest. In typical cases this is not difficult, but the milder varieties of oxycephaly, such as those reported in this paper, have been frequently overlooked, and they, like the severe types, may lead to blindness, though less frequently. The child oxycephalic should be subjected to frequent ophthalmoscopic examination and simple tests for visual acuity. If the optic disks reveal increasing choking or atrophy considered to be progressive, then decompression should be immediately carried out. When atrophy is advanced, little benefit is to be expected, but complete blindness may be prevented in some cases. As Sharpe noted a disappearance of convulsions and severe headache after decompression, these symptoms may be a very occasional indication for operation.

In conclusion, the cruciform linear craniectomy carried out by Faber and Towne (16) on an alleged oxycephalic, aged six months, may be mentioned. Two narrow strips of bone were removed in a direction parallel to the sagittal and coronal sutures respectively. Two and a half years later the shape of the head was almost normal, and no visual defect was manifest. Although it is doubtful that this child was a true oxycephalic, this operation, devised primarily to prevent the onset of severe cranial deformity, would appear to merit further trial in suitable cases.

I am much indebted to Dr. G. Riddoch and Mr. H. W. B. Cairns for their interest and advice and for their permission to publish the cases, and to Dr. M. H. Jupe for his interpretation of the radiograms.

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FIG. 1. Case I. The ocular signs, described in the text, are well seen



FIG. 2. Case I. Well-marked *crista sagittalis*. Convolutional atrophy

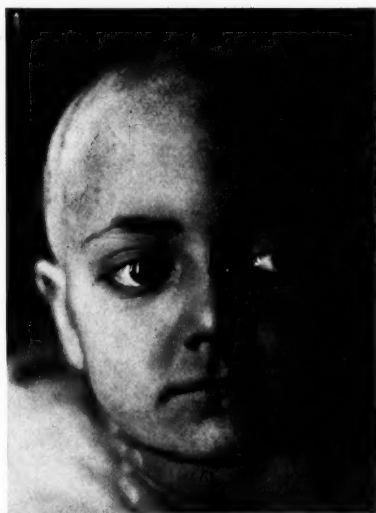


FIG. 3. Case II. Before operation, showing *crista sagittalis*, prominent eyes and ptosis





FIG. 4. Case II. Pronounced convolutional atrophy. No sutures visible



FIG. 6. Case III. Extreme convolutional atrophy. Absence of suture lines



FIG. 5. Case III. Nasal obstruction. Facies otherwise almost normal

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## THE PLASMA PROTEINS AND CARDIAC OEDEMA<sup>1</sup>

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### *Introduction*

IN spite of much intensive work the factors responsible for the production of oedema, including that of cardiac origin, are not yet understood. One of the fruitful lines of research of recent years has been the investigation of the role of the plasma proteins in the causation of oedema.

Richard Bright first drew attention to the fact that the oedema of the disease now named after him was accompanied by a deficiency in the plasma proteins. 'If the blood is drawn it is often buffed, or the serum is milky and opaque; and nice analysis will frequently detect a great deficiency of albumin' (7). The significance of this fact was not appreciated for many years, and it was almost a century later that Epstein (12) published the first of a series of papers in which he showed that this plasma protein deficiency was one of the principal factors in the causation of renal oedema.

Since Epstein's original publication in 1912 intensive studies of the plasma proteins have been made in many diseases, and included in these studies have been cases of cardiac cedema. Many such cases have been studied on the continent, and in 1932 Payne and Peters (27), in America, published the results of their studies in twenty-four patients with heart disease in various stages of decompensation. In this country no such study has yet been published, although isolated cases have been referred to in the course of papers on other forms of oedema, and it is the purpose of this paper to give the results of an investigation into the plasma proteins in a series of patients suffering from heart disease both with and without oedema. It is not suggested that the plasma protein deficiency which has been found to exist in cardiac oedema is the sole cause of the oedema in such cases, but it is suggested that such a deficiency is one of the factors.

### *Methods*

Ten c.c. of blood were withdrawn from an antecubital vein, care being taken to avoid stasis or haemolysis. Having been oxalated the specimen

<sup>1</sup> Received September 4, 1934.

was centrifuged within a quarter of an hour, and all estimations were carried out on the plasma. Duplicate estimations were done in order to ensure accuracy, and any sample that had undergone haemolysis was discarded. The actual estimation was carried out immediately after centrifuging in the majority of cases. Occasionally, owing to the exigencies of hospital routine, this was not possible, and in such cases the estimation was carried as far as the stage of the micro-Kjeldhal process, and then laid aside for a few hours.

The plasma having been obtained, 1 c.c., 2 c.c., and 4 c.c. were accurately pipetted into volumetric flasks of respectively 10 c.c., 20 c.c., and 20 c.c. capacity. The plasma in the 10 c.c. flask was made up to volume with distilled water, shaken well, and 1 c.c. of the diluted plasma (equivalent to 0.1 c.c. of plasma) was taken and its total nitrogen estimated by the ordinary micro-Kjeldahl process.

To the 20 c.c. flask containing 2 c.c. of plasma were added a few c.c. of distilled water, 2 c.c. of 10 per cent. sodium tungstate, and 2 c.c. of 2/3 N sulphuric acid, thus precipitating the proteins. Distilled water was then added to the 20 c.c. mark, the whole shaken and filtered. Of the filtrate 10 c.c. were taken (equivalent to 1 c.c. of plasma) and the nitrogen content again estimated by the micro-Kjeldahl method, thus obtaining the non-protein nitrogen.

In the remaining 20 c.c. flask sufficient solid magnesium sulphate was placed to saturate the 4 c.c. of plasma, and the sample then made up to volume with a saturated solution of magnesium sulphate, thus precipitating the globulin. The specimen was then shaken well, allowed to stand for a time and filtered. 1 c.c. of the filtrate (equivalent to 0.2 c.c. of plasma) was then used to estimate the nitrogen content.

By the following simple calculation it was possible to estimate the amount of globulin, albumin, and total protein in the sample:

*Calculation.* (Total nitrogen - non-globulin nitrogen)  $\times$  6.25 = globulin.  
(Non-globulin nitrogen - non-protein nitrogen)  $\times$  6.25 = albumin. It was not considered necessary to estimate the fibrinogen separately, and by this method it is included in the figure for the globulin.

It was originally intended to estimate the colloid osmotic pressure of the blood as well as the protein content, but, in view of the unanimity with which Govaerts' figures (16) have been accepted and confirmed, it was decided that this was not necessary, and that results equally accurate would be obtained by calculating the colloid osmotic pressure from the figures supplied by Govaerts.

### *Materials*

The cases upon which this study is based were all patients in the wards of the Royal Infirmary, Edinburgh, under the charge of Professor W. T. Ritchie. Fifty-four patients in all were studied, including eighteen cases of heart failure with oedema, sixteen cases of heart disease unaccompanied by

oedema, six cases of Bright's disease, four cases of tuberculosis, a miscellaneous group of seven cases, and three junior members of the hospital staff who were used as 'normals'. In many of the cases repeated examinations of the plasma proteins were made, so that in all the plasma proteins were estimated on eighty-seven occasions.

### Results

*Normals.* Three junior members of the hospital staff, all males in the third decade and all with good health records, were taken as 'normals', and the results are shown in Table I, from which it will be seen that our results

TABLE I  
*Normal Plasma Proteins*

No.	Total protein.	Albumin.	Globulin.	Alb./Glob.	Osmotic pressure.
	%	%	%		cm. H <sub>2</sub> O
60	7.490	4.925	2.565	1.920	42.14
61	7.126	4.813	2.313	2.081	40.80
62	6.738	4.175	2.563	1.629	36.48
<i>Average</i>	7.118	4.637	2.480	1.877	39.81
Moore and Van Slyke (1930)	7.1	4.3	2.8	1.53	—
Linder, Lundsgaard, and Van Slyke (1924)	6.73	4.11	2.61	1.57	—
Salvesen (1926)	7.0	—	—	1.67	—
<i>Grand average</i>	6.99	4.35	2.63	1.66	—

are in close agreement with those of other workers. For this reason it was not considered that a large number of cases was necessary to establish a normal. The normal protein content of the plasma is thus 7.12 gm. per cent., of which 4.64 gm. per cent. is albumin and 2.48 gm. per cent. globulin, resulting, according to Govaerts' (16) figures, in an osmotic pressure of 39.8 cm. of water. This, again, is in close agreement with other workers, e.g. Govaerts (15), 35–40 cm. water; Meyer (25), 35.5 cm. water (average); Iversen and Nakazawa (18), 32.5–40.1 cm. water; Fellows (14), 32.1–38.0 cm. water; Schade and Clausen (29), 31.37 cm. water; Mayrs (24), 40 cm. water; Verney (35), 36.7 cm. water. The fact that different workers, using different methods, should have achieved such consistent figures is strong proof in support of the correctness of the figures given for the colloid osmotic pressure of normal blood.

*Cardiac failure with oedema.* Thirty-two estimations were made in eighteen cases of cardiac failure with oedema, and the results are shown in Table II, from which it will be seen that the total protein varied from 3.14 to 7.20 gm. per cent., with an average of 5.28 gm. per cent., the albumin varying from 1.64 to 3.81 gm. per cent., average, 2.69 gm. per cent., while the globulin maximum was 4.38 gm. per cent., the minimum 1.5 gm. per cent., and the average reading 2.59 gm. per cent. The calculated osmotic pressure varied from 15.32 to 33.97 cm. of water, with an average of 25.32.

Cases No. 4 and No. 15 of Table II are of special interest, as in both the total protein content of the plasma was above 7.0 grm. per cent., while the osmotic pressure was low in both cases. The explanation lies in the fact

TABLE II  
*Cardiac Failure with Oedema*

No.	Disease.	Oedema.	Total protein.	Albumin.	Globulin.	Alb./Glob.	Osmotic pressure (calculated).
			%	%	%		cm. H <sub>2</sub> O
1	Mitral stenosis	++++	5.888	2.638	3.250	0.812	26.23
2	Mitral stenosis. Auricular fibrillation	+++	4.913	2.413	2.500	0.965	23.07
3	Chronic myocardial failure	+++	5.163	2.944	2.219	1.327	26.52
		++	6.150	3.025	3.125	0.968	28.90
4	Chronic myocardial failure	+++	5.401	2.588	2.813	0.920	24.84
		++	5.763	2.888	2.875	1.005	27.38
		+	6.163	2.850	3.313	0.860	27.95
		++	6.050	2.800	3.250	0.862	27.45
		++	5.421	2.608	2.813	0.927	25.15
		+++	7.200	2.825	4.375	0.646	29.74
5	Chronic myocardial failure	+++	3.725	1.975	1.750	1.129	18.30
		++	3.775	1.713	2.062	0.831	16.94
		+	4.725	2.850	1.875	1.520	25.15
6	Chronic myocardial failure	++++	5.732	2.669	3.063	0.871	26.10
		+++	4.550	2.925	1.625	1.800	25.22
		++	5.501	3.813	1.688	2.259	32.04
7	Mitral Stenosis	++++	5.863	2.488	3.375	0.737	25.34
		+++	5.075	2.575	2.500	1.030	24.29
		++	5.782	2.969	2.813	1.055	27.87
8	Aortic incompetence. W.R. negative	Trace	4.863	2.363	2.500	0.945	22.69
		+	4.813	3.250	1.563	2.080	27.55
9	Mitral stenosis	+	6.000	3.000	3.000	1.000	28.47
10	Chronic bronchitis. Cardiac failure	++	5.900	2.900	3.000	0.967	27.72
11	Mitral stenosis. ? Subacute bacterial endocarditis	++	5.420	2.670	2.750	0.971	25.49
12	Arteriosclerosis. Cardiac failure	+++	5.038	3.413	1.625	2.100	28.90
13	Mitral stenosis. Auricular fibrillation	+	5.100	3.000	2.100	1.429	26.72
14	Chronic myocardial failure	Trace	5.525	2.775	2.750	1.009	26.19
15	Chronic myocardial failure. Auricular fibrillation	++	7.100	3.600	3.500	1.029	33.97
16	Mitral stenosis	+	3.144	1.644	1.500	1.096	15.32
17	Aortic incompetence.	+	5.138	1.919	3.219	0.596	20.75
18	Carcinoma of stomach. Arterio- sclerosis. Chronic myocardial failure	+++	4.069	2.038	2.031	1.003	19.33
		++++	4.075	1.919	2.516	0.890	18.67
	<i>Average</i>		5.282	2.689	2.593	1.114	25.32
	<i>Maximum</i>		7.200	3.813	4.375	2.259	33.97
	<i>Minimum</i>		3.144	1.644	1.500	0.596	15.32

that in both cases the albumin content was low, while the globulin was well above the normal. This is a typical example of how misleading a simple estimation of the total protein content of the blood may be in drawing deductions as to the colloid osmotic pressure. A 'normal' figure for the

total protein may be accompanied by a much diminished osmotic pressure, due to a predominance of the globulin fraction.

Moore and Van Slyke (26) have shown that in glomerulonephritis the 'critical' level for the plasma albumin is 2.5 grm. per cent.—if the albumin falls below this level oedema occurs. A study of Table II shows that the 'critical' level in cardiac oedema is 3.2 grm. per cent., for of the cases with

TABLE III  
*Cardiac Failure without Oedema*

No.	Disease.	Oedema.	Total protein. %	Albumin. %	Globulin. %	Alb./Glob. %	Osmotic pressure (calculated). cm. H <sub>2</sub> O
19	Aortic incompetence	—	5.633	3.633	2.000	1.832	31.52
20	Myxoedema. Angina pectoris	—	6.476	3.913	2.563	1.527	34.50
21	Auricular fibrillation and flutter	—	6.126	3.188	2.938	1.085	29.77
22	Angina pectoris	—	5.700	2.825	2.875	0.983	26.91
23	Arteriosclerosis	—	6.619	3.838	2.781	1.380	34.36
24	Arteriosclerosis	—	8.713	4.838	3.875	1.249	44.03
25	Arteriosclerosis	—	6.363	3.738	2.625	1.424	33.30
		—	6.400	3.525	2.875	1.226	31.18
		—	6.213	3.744	2.469	1.516	33.04
26	Arteriosclerosis. Osteoarthritis	—	6.519	3.019	3.500	0.863	29.59
27	Mitral stenosis. Auricular fibrillation	—	5.613	3.238	2.375	1.363	29.05
28	Subacute bacterial endocarditis. Aortic incompetence	—	5.150	2.731	2.419	1.129	25.31
29	Auricular fibrillation	—	6.138	3.888	2.250	1.728	33.70
30	Chronic interstitial nephritis. Cardiac failure	—	5.900	4.000	1.900	2.105	33.87
31	Chronic interstitial nephritis. Cardiac failure	—	7.200	3.800	3.400	1.118	35.28
		—	5.781	3.281	2.500	1.312	29.61
32	Cerebral haemorrhage. Atheroma	—	6.631	3.350	3.281	1.021	31.66
		—	6.469	3.750	2.719	1.379	33.58
33	Arteriosclerosis	—	7.188	3.488	3.750	0.917	33.24
34	Arteriosclerosis	—	5.798	3.485	2.313	1.506	30.79
		—	6.800	3.425	3.375	1.015	32.41
		—	6.706	3.456	3.250	1.063	32.40
		—	5.650	3.525	2.125	1.659	30.72
5	Chronic myocardial failure	—	5.900	2.400	3.500	0.686	24.92
6	Chronic myocardial failure	—	5.238	3.644	1.594	2.286	30.58
		—	5.857	4.013	1.844	2.176	33.85
16	Mitral stenosis	—	7.481	3.106	4.375	0.710	31.95
17	Aortic incompetence	—	5.394	1.831	3.563	0.514	20.75
		—	5.932	3.244	2.688	1.207	29.70
	<i>Average</i>		6.340	3.555	2.785	1.320	32.17
	<i>Maximum</i>		8.713	4.838	3.875	2.105	44.03
	<i>Minimum</i>		5.150	2.731	1.900	0.863	25.31

cardiac oedema 87.5 per cent. had a plasma albumin content of less than 3.2 grm. per cent. Similarly the 'critical' level for the colloid osmotic pressure of the blood is 29 cm. water, 91 per cent. of the cases in this group having a figure below this level.

*Cardiac disease without oedema.* Sixteen cases were investigated, on whom twenty-nine estimations of the plasma proteins were made. All were

admitted to hospital on account of signs and symptoms referable to cardiac involvement. The results are shown in Table III, from which it can be seen that the average reading for the total plasma protein was 6.34 gm. per cent., the minimum being 5.15 and the maximum 8.71 gm. per cent. The corresponding values for the plasma albumin were 3.56, 2.73, and 4.84 gm. per cent. respectively, while in the case of the colloid osmotic pressure the results were 32.17, 44.03, and 25.31 cm. of water respectively. In several cases the same patient appears in both Table II and Table III, the reason being that during their stay in hospital the oedema completely disappeared and so they fell into both categories.

TABLE IV  
*Miscellaneous*

No.	Disease.	Oedema.	Total protein.	Albumin.	Globulin.	Alb./Glob.	Osmotic pressure (calculated).
			%	%	%		cm. H <sub>2</sub> O
35	Chronic myelogenous leukaemia	—	7.513	4.263	3.250	1.312	38.48
36	Syphilitic anaemia	—	7.176	3.238	3.938	0.822	32.09
37	Pernicious anaemia	—	4.987	3.706	1.281	2.890	30.44
38	Chronic arthritis	—	6.280	3.590	2.690	1.335	32.31
39	Duodenal ulcer	—	6.760	4.450	2.310	1.927	38.06
40	Diabetes mellitus	—	6.244	4.119	2.125	1.938	31.06
41	Chronic bronchitis	—	7.088	4.463	2.265	1.700	38.77
	<i>Average</i>		6.578	3.975	2.603	1.703	34.46
	<i>Maximum</i>		7.513	4.463	3.938	2.890	38.77
	<i>Minimum</i>		4.987	3.238	1.281	0.822	30.44

Taking the 'critical' level for albumin as being 3.2 gm. per cent., it is found that in this group 87 per cent. of the readings are above this value, while with a 'critical' level for the colloid osmotic pressure of 29 cm. of water, 91 per cent. of the calculated values are above this level. It is not suggested that there is anything specific about these 'critical' levels, but it is nevertheless a striking fact that in the case of the albumin level, 87 per cent. of the cases are below this level, while 87 per cent. of the cases without oedema are above it, and similarly with the colloid osmotic pressure that 91 per cent. of the cases with oedema are below this level and 91 per cent. of the cases without oedema are above it.

*Miscellaneous group.* The results in this group, recorded in Table IV, show that the average value for the total plasma proteins was 6.58 gm. per cent., with a maximum of 7.51 and a minimum of 4.99 gm. per cent. The corresponding values for the plasma albumin are 3.98, 4.46, and 3.24 gm. per cent., while for the colloid osmotic pressure they are 34.46, 38.77, and 30.44 cm. of water respectively. Here, again, the values for both the plasma albumin and the colloid osmotic pressure are all above the 'critical' level.

*Tuberculosis.* In this group seven observations were made on four cases.

The results (Table V) show that for the group as a whole the average reading for the total plasma protein is 5.40 grm. per cent., with a maximum of 6.26 and a minimum of 4.51 respectively, while the corresponding values for the plasma albumin are 3.01, 4.18 and 2.59 grm. per cent. respectively, and for the globulin 2.35, 3.13, and 1.63 grm. per cent. respectively.

TABLE V  
*Tuberculosis*

No.	Disease.	Oedema.	Total protein.	Albumin.	Globulin.	Alb./Glob.	Osmotic pressure (calculated).
			%	%	%		cm. H <sub>2</sub> O
43	Generalized tuberculosis	Ascites	4.506	2.881	1.625	1.773	24.89
		Ascites	4.588	2.588	2.000	1.294	23.41
		Ascites.	5.331	2.706	2.625	1.031	25.52
		Oedema of legs					
		Ascites.	4.632	2.694	1.938	1.390	24.90
44	Mitral stenosis. Pulmonary tuberculosis	—	6.263	3.200	3.063	1.045	30.10
45	Tubercular pleurisy	Pleural effusion	6.263	3.138	3.125	1.004	29.75
46	Tubercular pleurisy	—	6.240	4.180	2.060	2.029	35.53
		Average	5.403	3.055	2.348	1.367	27.61
		Maximum	6.263	4.180	3.125	2.029	35.53
		Minimum	4.506	2.588	1.625	1.004	23.41

TABLE VI  
*Renal Oedema*

No.	Disease.	Oedema.	Total protein.	Albumin.	Globulin.	Alb./Glob.	Osmotic pressure (calculated).
			%	%	%		cm. H <sub>2</sub> O
47	Acute nephritis	—	5.900	4.200	1.700	2.471	34.98
48	Acute nephritis	—	7.751	4.063	3.688	1.102	37.83
49	Acute nephritis	+	5.126	2.563	2.563	1.000	24.32
50	Subacute nephritis	—	6.301	3.113	3.188	0.976	29.69
		+++	4.060	2.250	1.810	1.243	20.49
		++	3.800	1.800	2.000	0.900	17.47
		+	3.775	1.775	2.000	0.888	17.28
		++++	4.182	1.369	2.813	0.487	15.81
51	Subacute nephritis. Uraemia	++++	4.182	1.369	2.813	0.487	15.81
52	Subacute nephritis	—	6.875	4.375	2.500	1.750	37.86

*Renal oedema.* There were six cases of glomerulonephritis in this group, on which nine observations were made. The results are shown in Table VI. In the cases of acute and subacute nephritis, unaccompanied by oedema, there was only a slight diminution in the plasma protein, and in the acute form the fall was entirely in the albumin fraction, there being an actual increase in the globulin fraction.

In the cases accompanied by oedema, however, both acute and subacute, there was a distinct fall in the plasma protein, this being much more marked in the subacute form, and once again the fall is most marked in the albumin fraction.

These results are in close agreement with those of other workers, and for this reason it was not considered necessary to investigate a larger number of cases, as this group was merely acting as a control to the cases of cardiac oedema.

### *Discussion*

It was Starling (31) who first drew attention to the importance of the fact that, although the osmotic pressure of the plasma proteins is so insignificant, yet it is of an order of magnitude comparable to that of the capillary pressure; and whereas the capillary pressure determines transudation, the osmotic pressure of the serum proteins determines absorption. Thus at any given time there must be a balance between the hydrostatic pressure of the blood in the capillaries and the osmotic attraction of the blood for the surrounding fluids.

Cushny (9) was of the opinion that filtration through the glomeruli was only possible if the hydrostatic pressure in the capillaries was greater than the osmotic pressure of the plasma proteins or, what the Germans have termed, the onkotic pressure of the blood. This has been confirmed by various workers, including White (36), who showed that in the frog the onkotic pressure was of such a magnitude as to be exceeded by the pressure in the glomerular capillaries.

Scott (30) came to the conclusion that every fall of blood-pressure resulted in an inflow of fluid into the blood-vessels, while every rise of blood-pressure resulted in an outflow of fluid. Similarly Zung and Govaerts (37) showed that dogs with low plasma proteins withstood large haemorrhages particularly badly.

This relationship was finally established experimentally by Landis (20), who showed that in mammals, as well as frogs, at the arteriolar end of the capillary the hydrostatic pressure exceeds the onkotic pressure, while at the venous end the reverse holds good, fluid passing from the tissues into the blood-stream. In this there is a regular and continuous fluid interchange between the blood and the tissues of the body. Landis had already found in the frog by direct measurement that the rate of movement through the capillary wall was directly proportional to the difference between the capillary pressure and the osmotic pressure of the plasma proteins, amounting to approximately 0.03 cubic micron per square micron of capillary wall per second.

It is thus evident that the plasma proteins, by means of their osmotic pressure, play a very considerable part in the fluid exchanges of the blood, and it only remains to summarize briefly the experimental evidence which

suggests the essential relationship between hypoproteinaemia and oedema. This experimental work is largely based on the process which Abel, Rowntree, and Turner (1) named 'plasmapheresis' and which they described as 'quantities of blood plasma may be withdrawn from an animal without apparent injury that exceed several times the maximum quantity of blood that can safely be drawn by the usual method of venesection, provided that the corpuscular element of the blood suspended in Locke's solution (0.6 per cent. sodium chloride) be returned to the vascular system after each bleeding'.

Leiter (21) demonstrated in dogs that oedema was always produced by plasmapheresis when the plasma proteins were maintained at or below 3 gm. per cent. In these experiments the oedema fluid had a protein content of less than 0.25 gm. per cent., and in his confirmatory experiments (22) he states that cardiac damage, starvation, and the alkalinity of the Locke's solution had all been controlled. Barker and Kirk (2), in a much smaller series of dogs and with a much slower plasmapheresis, obtained a gradual decrease in the serum proteins, particularly the albumin fraction, and whenever the albumin fell below 0.8 gm. per cent. oedema appeared. Darrow, Hopper, and Cary (10), also working on dogs, found the critical level for the total proteins to be 3-3.5 gm. per cent., while for albumin it was 1.5 gm. per cent. Similar results are reported by Lepore (23) who, however, tends to minimize the importance of the hypoproteinaemia, and to refer to the oedema thus produced as a sodium chloride oedema. He does not claim, however, that sodium chloride alone would have produced the oedema, and it is evident from his protocols that plasma protein depletion was required in each case before oedema began to occur, so that there would seem to be little doubt that the hypoproteinaemia was the primary factor and the sodium chloride content a secondary, though important, factor.

The results of Barnett, Jones, and Cohn (3) are of special interest as they emphasize a point which is probably of considerable significance in the aetiology of clinical oedema. Removing only small amounts of blood—25-100 c.c.—daily they found no significant drop in the plasma protein concentration and no oedema. As a result of their experiments they suggest that the loss of considerable amounts of protein is not alone sufficient to produce lowering of the level of the plasma proteins and that in nephritis of the degenerative type there may be an associated interference with the mechanism of regeneration.

*Cardiac oedema.* Epstein (12) reported twelve cases of cardiac oedema which he divided into two groups. In four of the cases the plasma proteins were only slightly diminished, the albumin fraction varying from 3.49 to 4.98 gm. per cent., and the globulin 1.99 to 2.54 gm. per cent. None of them apparently had any oedema, and he adds 'A moderate state of dilution or hydraemia would account for these values'. In the other eight there was a greater diminution in the total proteins, and the globulin was less

diminished than the albumin. Two of this latter group were cases of 'chronic myocarditis with anasarca', and the figures for them were respectively—albumin 1.81 grm. per cent., globulin 1.93 grm. per cent., and albumin 1.37 grm. per cent., globulin 2.04 grm. per cent. Of the first group he says there is a moderate dilution of the blood (true hydraemia); the proteins retain their normal proportions. The second group he sums up by pointing out that the total proteins are moderately or markedly reduced, especially the albumin, so that the globulin may predominate and there is oedema. The change in the quantitative relations of the serum protein is not due to hydraemia. In a later publication (13) he gives the average composition of the blood in 'cardiac condition' as—albumin 4.42 grm. per cent., globulin 2.24 grm. per cent., compared with his 'normal' of albumin 4.66 grm. per cent., globulin 2.74 grm. per cent. It is thus evident that in this latter publication he has not divided his cardiac cases into an oedematous and non-oedematous group.

One of the most comprehensive studies has been that of Govaerts. In his first paper (15) he says 'l'œdème de stase', the result of local circulatory trouble or cardiac inefficiency, when moderate, may not be accompanied by any alteration in the osmotic pressure of the proteins. But this is not the rule, and oftener, when such oedema is present, the osmotic pressure of the proteins is low. Every time the osmotic pressure, due to the proteins, was below 30 cm. (of water) oedema was present. In his 'cardiopathie avec nephrite de stase', with marked oedema, the onkotic pressure was low—25.5–16.5 cm. of water as compared with a 'normal' of 35–40 cm. of water. In a subsequent paper (17) he confirms these results and gives one case of mitral disease and auricular fibrillation with marked oedema, in which the onkotic pressure was 21.6 cm. of water, the albumin being 1.73 grm. per cent., and the globulin 4.83 grm. per cent.

Cope (8), who included a few cardiac cases in his study of nephritic oedema, reported that the plasma protein osmotic pressure in oedema from myocardial failure was only slightly reduced, and was markedly higher than in cases presenting a comparable degree of oedema of renal origin. His series includes eight cases of cardiac oedema, and the onkotic pressure varied from 20.2 to 39.9 cm. of water, compared with his normal of 30–32 cm. of water.

Iversen and Nakazawa (18), in a larger series, were of the opinion that in patients with cardiac oedema there is always a lowering of the onkotic pressure. Their figures varied from 17.3 to 36.3 cm. of water, there being only two cases of over 30.0 cm. of water, as compared with a normal figure of 32.5–40.1 cm. of water.

Payne and Peters (27), in a separate study of the serum proteins in heart disease, which included sixteen cases with oedema, found that the albumin varied from 2.89 to 5.83 grm. per cent. and the globulin from 1.17 to 2.94 grm. per cent., and in every case except one the total protein concentration was less than 7.0 grm. per cent.

Meyer (25) and Eppinger (11) also reported a lowering of the colloid osmotic pressure in cardiac oedema, and Eppinger emphasized the increase in the globulin fractions.

On the other hand there is the very definite but entirely unsupported statement of Moore and Van Slyke (26), in the course of a discussion on nephrotic oedema that 'It is well known that the oedema of heart failure is not attributable to plasma protein deficiency', while Tareev and his co-workers (33) also state that in cardiac decompensation, oedema is not accompanied by a drop in the onkotic pressure of the plasma proteins.

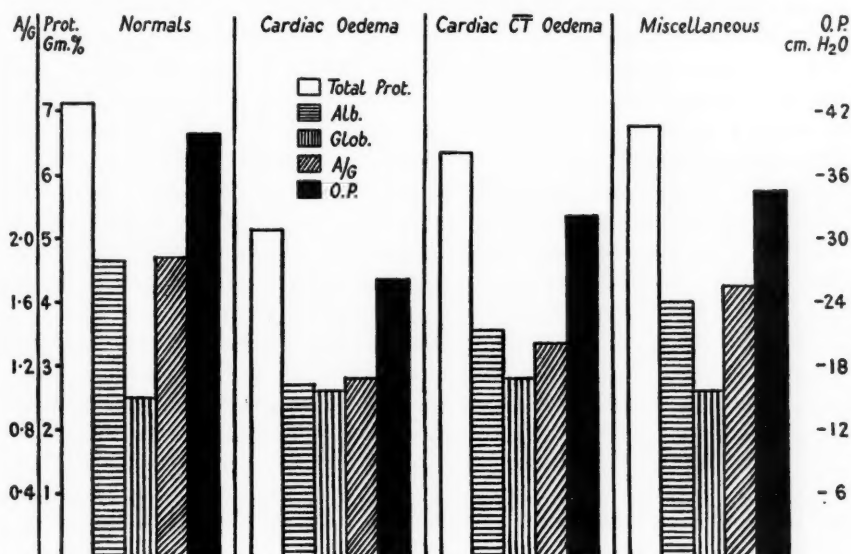


FIG. 1. Average figures in the different groups.

It is thus evident that what work has been done on the subject is in agreement with our own results, which show that in cardiac oedema there is a distinct fall in the plasma protein concentration. That this diminution is not merely an accompaniment of heart disease is shown by a comparison of the results in the group of cardiac cases with oedema and those without oedema, for, whereas in the cases with oedema 91 per cent. have an onkotic pressure less than 29 cm. of water, of the cases without oedema 91 per cent. have an onkotic pressure greater than 29 cm. of water. The position is shown graphically in Fig. 1, which records the average results in the two cardiac groups, the normal group and the miscellaneous group, and from which it can be seen that of these four groups the most striking fall in the plasma protein concentration is in the 'cardiac oedema' group, with a smaller diminution in the 'cardiac without oedema' group, while the 'miscellaneous' group occupies a position between the non-oedematous cardiac group and the normal figures.

*The significance of the low plasma protein concentration in cardiac oedema.* It is generally recognized that no one factor plays a dominant role in the causation of cardiac oedema, the importance of any one factor varying from case to case. The importance of the plasma proteins lies in their relation to the capillary pressure.

One of the main factors in the control of fluid exchanges between the bloodstream and the tissues is this balance which exists between the hydrostatic pressure tending to drive fluid into the tissues and the onkotic pressure tending to draw fluid into the blood-vessel. This balance can naturally be upset in one of two ways, either of which will result in an increased passage of fluid into the tissues: (i) the hydrostatic pressure may be raised, the onkotic pressure remaining unaffected; (ii) the onkotic pressure may be lowered, the capillary pressure remaining normal. Between these two extremes any modification may occur. In nephrotic oedema there is a marked fall in the onkotic pressure, the capillary pressure remaining comparatively unaffected, while in cardiac oedema there is a fall in the onkotic pressure, though not so marked as in nephrotic oedema, as well as a rise in the capillary pressure. In both, though attained by different methods, there is a preponderance of hydrostatic pressure over onkotic pressure, the result of which can only mean oedema.

This explains why the plasma proteins, and consequently the onkotic pressure, are at a higher level in cardiac oedema than in nephrotic oedema. It is also one of the reasons why anomalous cases of cardiac oedema may occur where there is only a slight diminution in the plasma protein, as in these cases there is such a marked rise in the capillary pressure that it only requires a slight fall in the onkotic pressure to result in such a preponderance of the hydrostatic pressure that oedema occurs. The other factor which undoubtedly plays a part is that of capillary permeability which, it is practically certain, is increased in these cases (19).

*The cause of the plasma protein deficiency in cardiac oedema. Blood-volume.* It has been suggested that the fall in the plasma proteins is more apparent than real, being largely accounted for by an increase in blood-volume. Such a view, however, is incompatible with the findings that, not only is there no correlation between the fall in the two protein fractions, but in the majority of cases there is an actual increase in the globulin fraction, the fall being entirely in the albumin fraction. Such a variation in the protein fractions could not be caused by a simple increase in blood-volume. Further, it is by no means decided yet whether there is a condition of hydraemia in cardiac oedema, in spite of Bolton's (6) findings, of hydraemic plethora developing into true plethora, and Rowntree and Brown's (28) reports of a 'simple hypervolaemia'. Strauss (32), for instance, was of the opinion that hydraemia occurs only in severe cases of cardiac decompensation; Veil and his co-workers (34) only found hydraemic plethora occasionally in their cases; Beckmann (4) concluded that the condition of the blood depended upon the degree of saturation of the tissues with water, while

Bock (5) could find no change in the amount of blood-plasma in cardiac disease.

*Albuminuria.* In view of the important part played by albuminuria in the depletion of the plasma proteins in renal oedema, it might be considered that a similar factor was responsible for the depletion of cardiac oedema. For this, however, there is no evidence. In none of our cases was the albuminuria extensive enough to account for the hypoproteinaemia, and in many of the cases there was never more than a trace of albumin in the urine.

*Transudation.* It is generally recognized that the protein content of the oedema fluid is higher in cardiac oedema than in nephrotic oedema, and might therefore be considered a possible explanation of the loss of protein from the blood. In nephrotic oedema such a possibility is definitely excluded, as the protein content of the fluid is so extraordinarily small. The figures in our cases, however, were not sufficient to account for more than a fraction of the protein depletion of the blood.

*Malnutrition.* In every case of cardiac decompensation there is a degree of malnutrition, the exact degree varying with the duration and severity of the illness. In malnutrition and cachexia, no matter what the cause, there is a tendency towards a fall in the level of the plasma proteins, and in nephritic oedema it is generally accepted that this is one of the factors in causing the plasma protein depletion. This malnutrition in cardiac disease is due partly to the disease itself, partly to the lack of sufficient protein intake, and partly to interference with protein formation. In view of the connexion which has been shown to exist between the liver and protein formation, it is not impossible that the chronic congestion of the liver which is such a common feature of cardiac decompensation, may actually interfere with protein regeneration. It is thus probable that this is the dominant factor in causing the plasma protein depletion in cases with cardiac oedema. A similar conclusion is reached by Payne and Peters (27), who tried to obtain an objective measurement of the degree of malnutrition by obtaining the weight of the patient before the illness, during the illness, and after the oedema had disappeared. 'The albumin deficits are due to malnutrition. The histories leave no doubt that anorexia is the chief cause of the malnutrition, with nausea and vomiting frequently acting as contributing factors.'

#### *Therapeutics*

The findings recorded here suggest a possible aid to the treatment of cardiac oedema. It has been part of the traditional treatment of cardiac decompensation to give the patient a very light diet, and particularly one which has a low protein content. The successful results obtained in the treatment of nephrotic oedema by means of a high protein diet, however, suggest that, if a plasma protein deficiency is one of the factors responsible for cardiac oedema, a high protein diet may also be of use in the alleviation of cardiac oedema. It may well be that many of these chronic cases of

cardiac oedema in the past, which have proved so resistant to treatment, have really been accentuated by the treatment they have received, in that the malnutrition from which they have been suffering has been steadily progressing and so increasing the plasma protein deficiency, which has thus come to occupy a more important part in the causation of the oedema. If such a patient had been given a diet containing the maximum of protein in addition to other treatment, there might very well have been a speedier and more satisfactory response to treatment. 'The common practice of restricting diet, and especially protein, in heart failure, may represent misdirected effort.' (Payne and Peters (27).)

Bearing in mind the digestive disturbances almost invariably present in these cases, patients with cardiac oedema should be given a diet containing the maximum of protein compatible with the digestive powers of the patient. Such a diet, containing an adequate proportion of protein and yet assimilable by the patient with cardiac oedema, can be easily obtained, and would prove of great value in helping to reduce the oedema in many cases. Even though there may be a marked albuminuria it is not necessary to restrict the protein, for there is no evidence that a high protein diet has an injurious effect on the kidneys. It is scarcely necessary to add that in such a diet the same restrictions must be observed as to salt and fluid as are at present observed.

#### *Summary*

1. The results are recorded of an investigation of the plasma proteins in fifty-four patients, consisting of eighteen cases of heart failure with oedema, sixteen cases of heart disease accompanied by oedema, six cases of Bright's disease, four cases of tuberculosis, a miscellaneous group of seven cases, and three junior members of the hospital staff who were used as 'normals'. In all, eighty-seven estimations were made.

2. There is a distinct diminution in the plasma proteins in cardiac oedema, 87.5 per cent. of the cases having a plasma albumin content of less than 3.2 gm. per cent.

3. In heart disease without oedema there is only a slight diminution in the plasma proteins as compared with the normal, 87 per cent. of the cases having a plasma albumin level greater than 3.2 gm. per cent.

4. In view of these findings it is suggested that plasma protein deficiency plays an important role in the aetiology of cardiac oedema.

5. The main cause for the plasma protein depletion in cardiac oedema is considered to be malnutrition.

6. It is suggested that the dietary of patients with cardiac oedema should contain the maximum amount of protein compatible with their digestive powers.

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EPILEPSY IN CYSTICERCOSIS (*TAENIA SOLIUM*)<sup>1</sup>

## A STUDY OF SEVENTY-ONE CASES

BY H. B. F. DIXON AND D. W. SMITHERS

(From the Queen Alexandra Military Hospital, Millbank)

With Plates 35 to 37.

INTEREST in human infestation with the larval form of *Taenia solium* Linnaeus 1758, has recently been considerably revived as the result of the work of Colonel W. P. MacArthur (1). For some years past he has called attention to the importance of this condition as a cause of epilepsy, particularly in soldiers who have served abroad. His account of the post-mortem changes in the parasites and the effects of these changes both in the late appearance of 'new cysts' and on the brain tissues, together with the description of the pathological changes in the brain, not only give a new conception of the pathogenesis of the disease, but are a revolutionary concept in parasitology as a whole. This work led to an investigation being carried out at the Queen Alexandra Military Hospital, Millbank. Prior to this, most of our knowledge of cysticercosis was derived from accounts of series of cases collected from the literature, the most recent series being those of Volovatz (2), Vosgien (3), and Schmitte (4). From time to time isolated cases have been reported in England, but no series has been published in English medical literature for many years.

The investigation carried out at Millbank has involved the examination of all patients with epilepsy or anomalous nervous symptoms: further, an attempt has been made to trace the later history of all cases of cysticercosis published in this country during the last forty years. This has afforded a unique opportunity of obtaining complete and documented histories of patients over a period of years, both before and after the onset of symptoms. Up to the beginning of July 1934, seventy-one cases have been traced, thirty-three of which had previously been recorded, five being published from Millbank during the course of the investigation. A study of the series of cases collected, together with a short general account of cysticercosis is the purpose of this paper.

Men may become the host of the larval form of *T. solium* by the ingestion of food or water contaminated directly by human excreta or indirectly by flies. As each tapeworm segment may contain from 30,000 to 50,000 eggs, the possibility that food or water may become contaminated in countries where sanitation is bad is obviously considerable. It is also possible for the

<sup>1</sup> Received August 1, 1934.

host of a tapeworm to infect himself either from his contaminated hands or clothing, or by regurgitation of segments into his stomach from his intestine. The hexacanth embryos pass into the blood-stream and may be carried to any part of the body.

The symptomatic classification adopted by Volovatz (2), Vosgien (3), and Schmitte (4) into groups according to the type of fit, or the character of other cerebral symptoms, is very misleading. A case of cysticercosis may show a variety of symptoms during the course of the disease, and one case examined at different times might possibly be placed in a different group on each occasion. The cysticercus tends to develop most frequently in the brain and muscles. During the early stages, the patient may have shown no symptoms of any kind, but many have a record of admissions to hospital for fever, general malaise, myalgia, &c., three or four months before the onset of the first nervous symptoms. The first symptom, however, may be severe and unaccountable headache.

Although a great variety of symptoms may occur, the majority of patients develop some form of epileptic attack. The initial nervous symptoms are followed in some cases by an interval of several months before they reappear, but later very few patients are free from fits or other nervous symptoms for any considerable period. The majority of our patients were adults at the time of their first fit, with no family history, or previous attacks suggestive of epilepsy.

A diagnosis of cysticercosis may be arrived at by demonstration of the larval form of *T. solium* in an excised cyst, by X-ray demonstration of calcified cysts, or by skin tests and complement fixation tests which, however, have not proved very satisfactory. As calcification occurs after the death of the parasite the time of its onset depends mainly on the longevity of individual parasites, so that radiological confirmation is unlikely within four or five years of infestation and may be further delayed. Radiological examinations may therefore have to be repeated over a period of years before a positive picture is obtained. Calcification of the cysts in the brain is less often seen and tends to occur at a later stage than elsewhere, so that a negative radiogram of the skull is common in cases showing heavy calcification in the muscles.

X-ray diagnosis is simple in cases where infestation is heavy and calcification advanced. It is important to realize that early calcification may be apparent only as small and very faint shadows, and at this stage even radiologists who have studied the disease may have to defer diagnosis until further deposition of calcium takes place. Further, in many cases cysts are so few that they are unlikely to be detected unless the X-ray examination includes the whole body. The X-ray appearances were worked out by Major W. K. Morrison (5). 179 of the cases investigated were X-rayed, 39 showed calcified cysticerci, 37 were doubtful and 103 negative. A description of the palpable nodules and the method of examination for them has already been given by the writers (6).

Up to July 1934 a total of 207 cases have been investigated, 170 of which have attended Millbank Hospital. The remaining 37 include patients who died before the investigation was started, and those X-rayed elsewhere, their films having been sent to the hospital for examination. Each patient was thoroughly investigated in order to exclude any other condition. The cerebrospinal fluid was examined in each case, and in only two of our positive cases was any abnormality found; Case 30 showed an increase in cells, 87 per cent. of which were lymphocytes, and 13 per cent. polymorphonuclear neutrophils, and Case 27 showed 24 cells per c.mm. all lymphocytes. In no case have we been able to demonstrate an eosinophilia in the cerebrospinal fluid, though eosinophils were present in Case 22 reported by A. G. Duncan and in Case 3 reported by R. Waterhouse. An eosinophilia in the blood is suggestive and is to be expected during the early stage of infestation, but a diagnosis is usually made late in the disease when the parasites are encysted and cut off from the general circulation. Case 27 is interesting in this connexion, as in 1932 before nodules were noted a differential white-cell count showed 12 per cent. of eosinophils, in 1934 when thirty nodules were easily palpable and the diagnosis was made eosinophils were 2 per cent., and a few months later when the nodules were perceptibly less tense and many could no longer be felt the eosinophils had risen to 14 per cent.

A study of the changes that take place in the cysts and in the brain goes far towards making the symptomatology of this condition comprehensible, and it is this work of MacArthur's that marks an advance in our knowledge and conception of cysticercosis.

The subcutaneous cysts tend to come and go singly or in crops and 'new' cysts may appear in any one patient over a period of years. The explanation lies in the fact that the death of the larva results in an increase in the fluid content of the cyst so that one originally flaccid and impalpable becomes tense and palpable. Absorption may take place at a varying period subsequently when it again becomes impossible to feel the cyst. It was found that palpable cysts removed contain dead larvae, the scolex being so adherent that it cannot be evaginated by digital pressure. This is the rule but is not invariably so, in one case a living parasite was removed from a site in the skin so superficial as to be palpable in its flabby undistended state.

Similar changes affect the parasites in the brain. These parasites cause little disturbance in the early stages, and the patient may live for years with numerous cysts in both cerebral hemispheres. After their death, however, the parasites may cause symptoms partly by their toxic effects and partly by their increase in size.

The cysticercus in the brain is surrounded by a wall of sclerosed neuroglia with a few small round cells and plasma cells between this area and the normal brain tissue. When the cysticercus dies and degeneration commences the tissues around also undergo active degenerative change. There

is an increase in cells and degeneration in the neuroglial tissue round the cyst. The damaged area may now undergo necrosis and again become surrounded by a wall of sclerosed neuroglia. In the brain of one man who had died in status epilepticus, after having fits for six years, it was found possible to demonstrate areas in each of these three main stages:

1. Cyst with sclerosed neuroglial wall.
2. Active degeneration.
3. Necrosed area with new sclerosed neuroglial wall.

This suggests that those cysticerci in stage 3 produced the fits during the last six years, those in stage 2 were responsible for the fits at the time of his death, and those in stage 1 were potential causes of further fits had he survived.

This sequence of events accounts for the great variety and variability of the symptoms that may be produced, as the cysts may be present in any numbers and any situations, and may die singly or in groups at various times. Calcification commonly commences in the scolex, so that in some cases cysts have been removed with a calcified scolex lying free in the cyst fluid. In most cases calcification follows absorption so that an elongated calcified body is produced, its shape depending on the pressure of the tissues in which it lies. Small round shadows may be seen when the scolex only has calcified, this is the form usually seen in the brain; an appearance of a halo may be produced when the calcium deposition is densest at the periphery of the cyst; and beaded or streaked shadows may occur when calcification has been preceded by caseation. The various forms that may be seen have been described and named by Morrison (5).

There is no known treatment for the established disease, in fact the administration of such substances as tartar emetic have in some cases produced an exacerbation of symptoms or a fresh crop of palpable nodules, presumably by causing the death of more parasites. The fits can usually be controlled to some extent by the use of luminal and bromides. Prophylaxis is of the greatest importance and must be directed towards the control of pork supplies, the treatment and supervision of patients harbouring *T. solium* and the proper disposal of their excreta. Infestation with this worm should be added to the list of notifiable diseases, and the host treated in hospital until the worm has been expelled. Patients should be warned of the danger of infecting themselves and others.

Apart from its scientific interest, a diagnosis of cysticercosis is of value for it removes the fear of familial epilepsy and prevents useless intracranial operation. A positive diagnosis is of especial value to a soldier in that it ensures a disability pension for those men who have served abroad.

The present series of seventy-one cases have all been in soldiers or their wives or children, and we have been unable to find a single case in English medical literature since 1892 that was not in a sailor, soldier, or soldier's family. Volovatz (4) noted that the condition was extremely common in the French colonial troops. There is no reason why persons pursuing other vocations should not become infected, but soldiers form the large majority

of patients of the hospital class returning to England from abroad, and the very nature of the communal life that they lead renders them particularly liable to infestation. It is to India that the largest number of soldiers are sent on foreign service, and it is there that the majority of our patients have been infested, but there is no real evidence that the disease is more common in India than in some other parts of the world. Sixty-five of our cases were in soldiers, two were the wives of soldiers, three the children of soldiers and one was a sailor. Two of our patients had never been abroad. The condition is probably far more common than has previously been believed, the greatest obstacle to correct diagnosis being the fact that the disease has been very largely forgotten in this country. It is a significant fact that since the present work was instituted and interest revived many new cases have been reported both in England and abroad; and despite the fact that this series includes all cases that we have been able to trace as far back as 1892 as many as thirty-six have been diagnosed during the past two years and all but fourteen since 1926. This series includes none of the many doubtful cases we have seen which, could not be proved to be suffering from cysticercosis at the time they were examined. Thirty-seven patients were marked as 'doubtful' radiologically pending further examination.

The diagnosis in the present series was made by examination of an excised cyst in twenty-two cases, by X-ray examination in thirty-one (seven of which were found accidentally when X-rayed for some other condition), by examination of an excised cyst and a positive X-ray finding at the same time in seven, at the post-mortem examination in five, at operation on the brain when cysticerci were found in two, on removal of a cyst from the eye in one case, by a positive complement fixation test together with a typical history of nodules that came and went in one case, and in another case six years after death when a brain specimen was re-examined.

Sixteen of these patients are dead, twelve died directly from the effects of cysticercosis, six in status epilepticus, two with meningeal symptoms, two with symptoms of cerebral tumour, one after operation for removal of cysts from the brain, and one suggesting 'some form of encephalitis'. Four died of intercurrent disease, seven died in asylums.

The shortest period between the onset of symptoms and death was six days (Case 41) and the longest twelve years (Case 7). In the majority of cases symptoms first appeared after the patient had been three or four years abroad, but in one case (Case 42) fits did not commence till twelve years after the patient had returned to England and hundreds of calcified cysts could be seen in the radiograms all over the body at the time of the first fit. In only five cases have the fits ceased.

1. *Case 2.* Fits for twelve years, then no fits for the last two years before being lost sight of.

2. *Case 12.* Fits for fourteen years, then no fits for the last four years, working as a barber.

3. Case 21. Fits for two years, then no fits for the last twenty-one years.

4. Case 34. Fits for three years, then no fits for twenty-four years till death from pneumonia, aged 60.

5. Case 37. Fits for thirteen years, then no fits for the last twenty-one years.

One patient (Case 35) has been having fits for twenty-eight years. Three patients found to be suffering from cysticercosis accidentally when X-rayed for some other condition state that they have never had fits of any kind (Cases 14, 71, and 36), and Case 32 X-rayed on account of a personal history of tapeworm, and epilepsy in his twin brother has also had no fits.

Nodules were noted before the onset of symptoms in six cases, in two for as long as four years before the first fit.

Papilloedema was seen in seven cases. Seven cases were operated on, in five cysticerci were removed from the brain, in one adhesions between meninges and brain were cut, and in the other a decompression was done, but fits continued in every case that survived. Three cases had cysticerci removed from the eye.

Thirteen patients gave a history of tapeworm infestation, eight of these were unidentified, four were found to be *T. solium* and one was stated to be *Taenia saginata*. Three others stated that they had had a tapeworm, but no record could be found on their documents to confirm this. It is not suggested that these worms were the source of the infestations in every case, only four were proved to be *T. solium*, and in some of the other cases the time of infestation with the adult worm is incompatible with the degree of calcification noted in the cysticerci on the assumption of auto-infestation. The husbands of two patients had had tapeworms (Case 6 unidentified and Case 24, *T. solium*), the twin brother of one case had had a tapeworm (Case 31 unidentified), a friend of another (Case 55, *T. solium*), and a man in the same regiment as another (Case 68 unidentified) had both had tapeworms. That is, five cases gave a history of contact with persons harbouring a tapeworm.

Intradermal tests were done by Dr. Hamilton Fairley in fifty-three cases, fourteen of which were in proved cysticercosis cases. Eight of these gave a negative reaction while six were positive. One other positive was found and was almost certainly a case of cysticercosis, no other definite confirmation, however, could be obtained. Complement fixation tests were done on the blood in fifty-seven cases, fourteen of which were proved cases of cysticercosis of which five were positive and nine negative, and complement fixation tests were done on the cerebrospinal fluid in twenty-three cases, three of which were proved cases of cysticercosis, with no positive results.

Twenty-three positive cases were never X-rayed, thirty-nine showed definite calcified cysticerci, four were doubtful and four negative.

### Summary

1. Cysticercosis (*T. solium*) is an important and not uncommon cause of nervous symptoms particularly fits, chiefly in patients who have resided abroad, but occasionally in those who have never been outside the British Isles.

2. The important symptoms of the disease result from the death of parasites in the tissues, singly or in groups, and as the number of parasites present and the situations they occupy may vary widely, the disease is therefore protean in its manifestations.

3. A diagnosis is established by demonstrating the calcified cysticerci in the radiograms or by finding the larval form of *T. solium* in excised cysts.

4. Though treatment of the established disease can only be palliative the diagnosis is important not only from a scientific point of view but also because a positive diagnosis of cysticercosis removes the fear of heredity attached to epilepsy, prevents operation on the skull where the end result is most unlikely to be successful, and in the case of a soldier who has served abroad ensures a disability pension.

5. In every case of epilepsy occurring in a patient with no family history of fits and no previous history of fits in childhood the possibility of cysticercosis should be entertained. Every person who develops fits for the first time after a period of residence abroad should be regarded as a possible case of cysticercosis until proved otherwise.

### APPENDIX

#### *Short Summary of 71 Cases of Cysticercosis (T. solium) 38 of which have Not Previously been Published*

*Case 1.* (P. H. Pye-Smith, *Brit. Journ. Dermat.*, Lond., 1892, iv. 366.) Served eight years in India and Burma. Severe headache commenced in April 1891, numerous nodules appeared in April 1892, two excised and larval form of *T. solium* found. Nervous symptoms (twitching of limbs and weakness) first appeared in 1894. Optic atrophy, and epileptiform fits 1897. Died in January 1904 in status epilepticus after six years in an asylum.

*Case 2.* (R. Waterhouse, *Quart. Journ. Med.*, Oxford, 1913, vi. 469.) Tapeworm (unidentified) followed by first fit in 1898, aged 22, after three years in India. Status epilepticus in 1906, nodules noted. 1908: nodule excised and larval form of *T. solium* found. Nodules for six years, fits for twelve years, then no further fits till lost sight of in 1912.

*Case 3.* (R. Waterhouse, *Quart. Journ. Med.*, Oxford, 1913, vi. 469.) 1909: first fit aged 27, one year after return from India where he had served five years. 1910: double optic neuritis, eosinophils in C.S.F. Nodule excised and larval form of *T. solium* found. Death from meningitis in 1912, 300 cysts found in brain at post-mortem examination.

*Case 4.* (G. E. Peachell, *Journ. Mental Science*, Lond., 1910, lxii, 180.) First fit December 1899, aged 26, one year after return from India where he had served for five years, nodules noted, frequent fits followed. 1902: nodule excised and larval form of *T. solium* found. 1916: died of pneumonia sixteen years after first fit after frequent admissions to asylum. Numerous cysts found in brain at post-mortem examination.

*Case 5.* (G. E. Peachell, *Journ. Mental Science*, Lond., 1916, lxii, 180.) 1902: first fit aged 26. Fits continued. 1914: maniacal, admitted to asylum and died in status epilepticus in 1915. Seventy cysts found in brain at post-mortem examination.

*Case 6.* (H. K. Abbott, *Lancet*, Lond., 1921, ii, 956.) Husband had tapeworm (unidentified). 1917: mental symptoms two years after return from India where she had been for eight years. 1918: nodules present, two local detachments of the retina. 1919: cysticercus removed from the eye. 1921: died in an asylum from pulmonary tuberculosis. Numerous cysts found in brain.

*Case 7.* (J. R. Hughes, *Lancet*, Lond., 1921, ii, 956.) 1917: first fit aged 29, three years after leaving India where he had served for six years. 1918: nodules noted, one excised and larval form of *T. solium* found. 20 per cent. eosinophils in blood. Nodules became painful when patient had a high temperature. Fits continued. June 1929: died in status epilepticus. Numerous cysts found in brain.

*Case 8.* (V. Coates, *Proc. Roy. Soc. Med.*, Lond., 1922-3, xvi, 28.) Tapeworm (unidentified). 1917: first nodule noted after three years in India. 1921: first fit, 14 per cent. eosinophils in blood. Fits continued. 1921: nodule excised and larval form of *T. solium* found. 1923: eosinophils 4 per cent. Fits continued till lost sight of in 1927.

*Case 9.* (J. A. Braxton Hicks, *Westminster Hosp. Reps.*, Lond., 1924-8, xx, 114.) 1916: first fit aged 24, one year after return from India where he had served for two years. Numerous fits, mental deterioration. 1922: died in status epilepticus, diagnosed multiple tuberculomata of brain *post mortem*. Six years after death sections of brain cut and larval form of *T. solium* found.

*Case 10.* (J. Rowe, *Journ. Royal Army Med. Corps*, Lond., 1925, xlv, 291.) 1923: tapeworm (*T. solium*) followed by 'eccentric behaviour', aged 23, in India. 1924: numerous nodules one excised and larval form of *T. solium* found. X-ray negative. 1925: first definite fit. 1933: constant fits, numerous nodules, mentally deteriorated.

*Case 11.* (R. Priest, *Brit. Med. Journ.*, 1926, ii, 471.) 1925: fever followed two months later by pain in muscles and appearance of nodules and one month later again by first fit, aged 24, after four years in India. Cyst in retina. Swelling of muscles. 1926: nodule removed and larval form of *T. solium* found. 1933: frequent fits, blind in left eye.

*Case 12.* (E. J. H. Roth, *Brit. Med. Journ.*, 1926, ii, 470.) 1915: first fit aged 31, four years after return from India where he had served for six years. Fits continued. 1926: calcified cysticercus found at bottom of discharging sinus. Radiograms showed numerous cysts all over body, some seen in brain. 1933: nodules present. Fits for fourteen years then no fits for past four years, works as a barber.

Case 13. (B. Weinbren and H. K. Graham-Hodgson, *Lancet*, Lond., 1926, ii. 174.) 1925: numerous calcified cysticerci seen when X-rayed for another condition twenty-three years after return from South Africa where he had been for eleven years. No record of fits. No further particulars could be traced.

Case 14. (J. F. Brailsford, *Proc. Roy. Soc. Med.*, Lond., 1926 (section Electro-Therap.), xix. 45.) Served seven years in India and three in South Africa. Numerous calcified cysticerci seen in radiograms taken for another condition twenty-three years after return to England. 1933: patient states that he has never had a fit of any kind.

Case 15. (J. F. Brailsford, *Proc. Roy. Soc. Med.*, Lond., 1926 (section Electro-Therap.), xix. 45.) Served in South African War; 1924: numerous calcified cysticerci found accidentally when X-rayed for some other condition. 1926: two calcified cysticerci removed from muscles. 1933: having minor epileptic fits.

Case 16. (W. M. Cameron, *Journ. Roy. Army Med. Corps*, Lond., 1928, i. 128.) 1922: first fit aged 22, after three years in India. 1923: numerous nodules, 13 per cent. eosinophils in blood. 1927: nodule excised and larval form of *T. solium* found. 1930: well-marked calcification seen in cysts in radiograms. 1932: three cysts removed from parietal region and one from motor cortex. 1933: still having frequent fits.

Case 17. (W. M. Cameron, *Journ. Roy. Army Med. Corps*, Lond., 1928, i. 128.) Tapeworm (unidentified). 1926: first nodule noted, diagnosed meningitis. Served in India, Egypt, and Sudan, from 1922 to 1928. 1927: nodule excised and larval form of *T. solium* found. Fits continued till last seen in 1933, nodules come and go.

Case 18. (W. Broughton-Alcock, W. E. Stevenson, and C. Worcester Drought, *Brit. Med. Journ.*, 1928, ii. 980.) 1923: first fit aged 23, after four years in India. Cysticercus removed from the eye 1924. Fits continued. Died in 1928. 100 cysts found in one cerebral hemisphere.

Case 19. (C. J. Hill Aitken, *Brit. Med. Journ.*, 1928, i. 943.) 1926: nodules noted after five years in India. 1928: first fit two years after return from India, nodule excised and larval form of *T. solium* found. Diagnoses suggested during that period were: encephalitis lethargica, neurasthenia, hysteria, pernicious anaemia, malingering and heart failure. Died in status epilepticus in 1930.

Case 20. (G. H. Dive, *Journ. Roy. Army Med. Corps*, 1929, liii. 371.) Born in India, first fit aged 22 in 1928. Numerous nodules 1929, one excised and larval form of *T. solium* found. Eosinophils in blood 1.5 per cent. March, 16 per cent. June. 1933: inmate of an infirmary, mentally deteriorated, still having fits.

Case 21. (W. Broughton-Alcock and B. Weinbren. *Proc. Roy. Soc. Med.*, Lond., 1930, xxiv. 222.) 1911: first fit after eight years in India. 1913: last fit. 1926: radiograms taken of leg wound and numerous shadows seen. 1934: numerous calcified cysticerci seen in radiograms all over body. Fits lasted only two years, no fits for last twenty-one years.

Case 22. (A. G. Duncan, *Med. Press and Cir.*, Lond., 1933, cxxxv. 423.) Tapeworm 1927 stated to be *T. saginata*. First fit 1927, aged 30, after two

years in India. Later diagnosed dementia praecox. 1928: nodules noted one excised and larval form of *T. solium* found. Eosinophils in C.S.F. 1929: thirteen cysts removed from pia mater. Died in status epilepticus six months later, fifty cysts found in brain at post-mortem examination.

*Case 23.* (H. B. F. Dixon, *Journ. Roy. Army Med. Corps*, Lond., 1933, lxi. 126.) 1926: first fit aged 21, after three years in India. Fits continued. 1930: nodules noted. 1933: numerous nodules one excised and larval form of *T. solium* found, radiologically positive. 1934: still having fits nodules present.

*Case 24.* (A. G. Duncan, *Med. Press and Cir.*, Lond., 1933, cxxxv. 423.) Husband had tapeworm (*T. solium*) at Cawnpore in 1927, one month after husband had noticed the worm patient had first fit, aged 32, after one and a half years in India. 1930: numerous fits, mentally deteriorated, admitted to an asylum. 1931: died in status epilepticus, numerous cysts found in brain at post-mortem examination.

*Case 25.* (H. B. F. Dixon, *Journ. Roy. Army Med. Corps*, Lond., 1933, lxi. 126.) 1927: one nodule noted. 1929: first fit aged 21, after two and a half years in India, followed by numerous fits interspersed with attacks of 'Myalgia'. 1933: Numerous nodules, one excised and larval form of *T. solium* found, radiologically positive. Spasticity of left leg, Kahn test positive. 1934: numerous fits, mentally and physically deteriorated.

*Case 26.* (D. Denny-Brown, *Proc. Roy. Soc. Med.*, Lond., 1934, xxvii. 667.) 1924: first fit aged 24, after service in India, unconsciousness followed by prolonged amnesia and then fits at irregular intervals, with periods of very frequent fits. 1931: optic atrophy. Right temporal decompression, no abnormality seen. Radiograms showed numerous calcified cysticerci in brain. 1933: still having fits.

*Case 27.* (H. B. F. Dixon and D. W. Smithers, *Journ. Roy. Army Med. Corps*, Lond., 1934, lxii. 426.) 1931: first fit aged 26, after four and a half years in India followed by headache, vomiting, and papilloedema. 1932: eosinophils in blood 12 per cent. 1934: numerous nodules, one excised and larval form of *T. solium* found. Eosinophils 2 per cent. Three months later nodules less tense, eosinophils 14 per cent., 24 cells per c.mm. in C.S.F. Still having fits.

*Case 28.* (S. Behrman, *Proc. Roy. Soc. Med.*, Lond., 1934, xxvii. 668.) Tapeworm (*T. solium*) 1926. First nodule 1927. First fit 1928. Numerous fits, Jacksonian with visual hallucinations and loss of memory. 1933: hundreds of calcified cysts seen in radiograms. 1934: major fits.

*Case 29.* (F. Holmes, *Journ. Roy. Army Med. Corps*, Lond., 1934, lxii. 296.) Tapeworm (*T. solium*) 1928. 1929: nodules noted. 1930: first fit. 1931: nodule excised and larval form of *T. solium* found, radiologically negative. 1933: still having fits, nodules present, radiologically positive.

*Case 30.* (E. B. Marsh, *Journ. Roy. Army Med. Corps*, Lond., 1934, lxii. 294.) 1930: headache and fever. 1931: 'delusional insanity' aged 28, after four years in India. Three months later, double optic neuritis, increased cells in C.S.F. later diagnosed disseminated sclerosis. 1932: died. Cysticercus meningitis, numerous cysts found in brain at the post-mortem examination.

*Case 31.* (W. K. Morrison, *Brit. Med. Journ.*, 1934, i. 13.) Son of a soldier, twin brother had a tapeworm (unidentified) first noticed in 1928. Fits in infancy aged 18 months and 3½ years. Third fit in 1931, aged 11, three years after return from India where he had been for two years. 1933: no nodules, has had further fits, radiologically positive. 1934: has had seven fits in all, increase in calcification noted in cysts seen in radiograms.

*Case 32.* (W. K. Morrison, *Brit. Med. Journ.*, 1934, i. 13.) Tapeworm (unidentified) first noticed in 1928 when returning from India where he had been for two years. 1933: radiologically positive when X-rayed with twin brother, Case 44, also positive. No fits, no nodules. 1934: still no fits, increase in calcification noted in cysts shown in radiograms.

*Case 33.* (S. F. Dudley, *Journ. Roy. Nav. Med. Ser.*, Lond., 1934, xx. 179.) 1933: first fit aged 40, after one year in China, having served in the Navy for twenty years. History of tapeworm (*T. solium*) calcified cysticerci seen in radiograms. Variation in aura and seizures. Wassermann reaction positive, syphilitic periostitis of right tibia, no improvement in fits on anti-syphilitic treatment.

*Case 34.* Tapeworm (unidentified). 1902: 'rheumatic fever followed by brain fever' aged 32, followed by fits for three years. 1932: diagnosed tabes and Charcot's disease right tarsus. Wassermann reaction negative. 1929: radiologically positive. 1929: died aged 60 from pneumonia having had no fits for twenty-four years. Diagnosis made by a study of his radiograms four years after the patient's death.

*Case 35.* Tapeworm (unidentified) in 1904. 1906: first fit aged 23, after two years in India. Fits continued. 1931: calcified cysticerci seen in radiogram taken for some other condition, patient was then thought to be a case of tabes, Wassermann reaction negative. Numerous nodules palpable. 1934: still having fits which have continued for twenty-eight years.

*Case 36.* Diagnosed by Capt. S. F. Dudley, R.N. Served in India 1906-12. Headaches relieved by glasses. No fits at any time. 1925: ruptured left thigh muscles and developed myositis ossificans. 1934: complained of return of pain in left thigh. Radiograms revealed numerous calcified cysticerci.

*Case 37.* 1910: first fit aged 21, after four years in India. 1930: diagnosed cysticercosis radiologically. 1933: no fits for last ten years after having fits for thirteen years.

*Case 38.* Diagnosed by H. Macdonald Critchley. 1915: first fit aged 24, shortly after leaving India where he had served for five years. Frequent fits since then. No nodules ever noticed. 1934: radiograms show calcified cysticerci in all parts, including the skull.

*Case 39.* 1918: first fit aged 31, nine months after return from India where he had served on and off for ten years. 1919: operated on and cyst removed from brain, larval form of *T. solium* found. 1933: nodules come and go, fits persist. Radiograms show suspicious shadows.

*Case 40.* 1922: first nodule noted after two years in India, first fit four years later, four years after returning from India. Diagnosed cysticercosis by Mr. Hugh Cairns in 1927 on excision of a cysticercus. Fits continued. Died in 1931, diagnosed lung tumour, no post-mortem examination.

*Case 41.* 1922: in Egypt having served one year previously in India, developed headache, general malaise and fever, aged 22. Became lethargic and developed signs of 'encephalitis', died in five days. At the post-mortem examination numerous cysticerci found in every part of the brain being much smaller than any seen in other brain specimens. Probably a recent hyperinfestation.

*Case 42.* 1923: first fit aged 39, twelve years after leaving India where he had served for seven years. Had not been out of England since 1923. Second fit 1933, when hundreds of well-calcified cysts were seen in radiograms of every part of the body, including brain, hands, and feet. 1934: no further fits, has only had two in all.

*Case 43.* 1925: first fit aged 24, after four years in India. Fits continued. Maniacal 1928, with Jacksonian fits. 1929: nodules noted one excised and larval form of *T. solium* found. At operation thirteen cysts removed from brain, died two days later. Sixty-six cysts found in brain at the post-mortem examination.

*Case 44.* 1926: first fit aged 24, after two years in India. 1932: numerous nodules which proved to be fibro-lipomata. Radiologically positive. Eosinophils in blood 8 per cent. 1933: status epilepticus for three days. 1934: still having fits, increase in calcification noted in radiograms.

*Case 45.* 1927: first fit aged 27, two years after leaving India where he had served for four years. At one time diagnosed meningitis. Treated at different times with 'radium to the head' and extraction of all teeth. 1933: nodules noted. 1934: radiologically positive.

*Case 46.* 1927: first fit aged 37, eleven years after leaving India, eight years after leaving Egypt, and three years after leaving Jamaica. 1929: Jacksonian fits. 1931: operation, dense adhesions between meninges and brain cut, seventeen months later no improvement, second operation more adhesions cut. Fits continued with spasms of right side and slurring of speech. 1934: radiologically positive.

*Case 47.* 1927: first fit aged 24, after five years in India, nodules noted soon afterwards. 1933: numerous fits since onset. Radiologically positive: 1934: fits more frequent, no nodules palpable, fresh calcified cysts seen in radiograms.

*Case 48.* Tapeworm (unidentified). 1927: first fit aged 25, one year after return from India where he had served for five years. Nodule on lip noticed a fortnight later. No further fits till 1929. 1930: nodule excised and larval form of *T. solium* found, radiologically positive. 1933: still having fits, marked calcification in cysts seen in radiograms, nodules still present.

*Case 49.* 1928: headache followed by first fit two months later, aged 24, after three years in India and China. Fits continued. 1934: one nodule palpated radiologically positive.

*Case 50.* Tapeworm (unidentified) in Sudan in 1929. 1930: first fit aged 23, after three years in India and one in Sudan, nodules present. Optic neuritis five months later. 1931: numerous fits, numerous nodules. 1933: still having fits, nodules come and go. Complement fixation and intradermal tests strongly positive in 1931.

*Case 51.* 1929: first fit aged 24, after one year in India. 1930: diagnosed melancholia. 1933: attacks of dizziness, no mental symptoms. Calcified cysticerci seen in radiograms of skull.

*Case 52.* 1929: nodules noted. 1930: first fit aged 22, one year after leaving India where he had served for five years. Fits mostly Jacksonian in type. 1932: nodule excised and larval form of *T. solium* found, radiologically positive. 1933: still having attacks with twitching of left leg, no major fits for six months.

*Case 53.* 1929: first fit aged 23, after three years in India, followed by two further fits. 1932: nodules noted. 1933: haemoptysis, tubercle bacilli found in sputum. Nodule excised and larval form of *T. solium* found. Eosinophils in blood 8 per cent. No fits between 1929 and 1933.

*Case 54.* 1927: severe headaches. 1929: first fit aged 29, four years after leaving India where he had served for six years. Fits numerous and severe, major and minor attacks, status epilepticus for three days in 1931. 1933: radiologically positive, still having fits.

*Case 55.* 1929: first fit aged 25, born in India. Constant fits followed. 1933: radiologically positive, no nodules found. A friend in his regiment was in hospital with tapeworm (*T. solium*) three months before patient had his first fit.

*Case 56.* Diagnosed by H. Macdonald Critchley. 1930: first fit aged 31, one year after return from India where he had served for seven years. Numerous fits since then. 1934: radiograms show numerous calcified cysticerci in limbs, trunk, and skull.

*Case 57.* 1930: first fit aged 25, having never been abroad. 1932: numerous nodules, larval form of *T. solium* found on excision, radiologically negative.

*Case 58.* 1930: first fit aged 24, after four years in India. No further fits till 1932. Third fit September 1933. Radiologically positive, obstinate, and difficult to manage.

*Case 59.* 1930: first fit aged 23, after two years in India. No further fits till December 1932. Frequent fits followed. 1933: eosinophils in blood 10.5 per cent., radiologically positive, no nodules present. 1934: two nodules found, still having fits.

*Case 60.* 1930: first fit aged 21, after nine months in India. 1933: still having fits, radiologically positive, no nodules found at any time.

*Case 61.* 1931: first fit aged 27, one year after leaving India, where he had served for five years. Major, minor, and Jacksonian attacks at different times. 1933: radiologically doubtful. 1934: radiologically positive.

*Case 62.* 1931: first fit aged 10, four years after leaving Bermuda where he had lived for three years. 1933: still having fits, otherwise quite normal, no nodules, radiologically positive.

*Case 63.* 1931: first fit aged 25, after five years in India. 1932: diagnosed cerebral tumour, operated on and cyst removed from brain, eight months later second operation, numerous cysticerci seen in brain, decompression only. 1933: headaches, but only one major fit since last operation.

*Case 64.* 1931: first fit aged 27, after three years in India. Fits continued. 1932: nodules noted. 1933: nodule excised and larval form of *T. solium* found.

*Case 65.* 1931: first fit aged 19½, one year after returning from India where he had served for four years. Nodules appeared five months later one excised and calcifying larval form of *T. solium* found. Eosinophils in blood 12 per cent., radiologically positive.

*Case 66.* 1932: first fit aged 22, after two years in India. One month later nodule removed from lower canthus, left eye, and larval form of *T. solium* found. 1933: radiologically negative.

*Case 67.* 1932: first fit while under treatment for tapeworm (*T. solium*) first noticed in 1931, aged 22 at the time of first fit, having served two years in India. Nodules noticed nine months later, one excised and larval form of *T. solium* found. 1934: no nodules, no fits for two months, X-ray report 'doubtful early calcifying forms seen'.

*Case 68.* 1932: first fit aged 25, after four and a half years in India. A friend in his regiment had a tapeworm (unidentified); 1933: still having fits, eosinophils in blood 8 per cent., radiologically positive.

*Case 69.* 1933: first fit aged 26, after five years in India. Radiologically negative. Two nodules found after careful search, one excised and larval form of *T. solium* found.

*Case 70.* 1933: one hour's automatism, aggressive and confused. Similar attack lasting only a few minutes a day later. Radiologically very suspicious. 1934: major epileptic attack, admitted to hospital in drowsy state. Radiograms show shadows originally seen and several new calcified cysticerci. Has never been outside the British Isles.

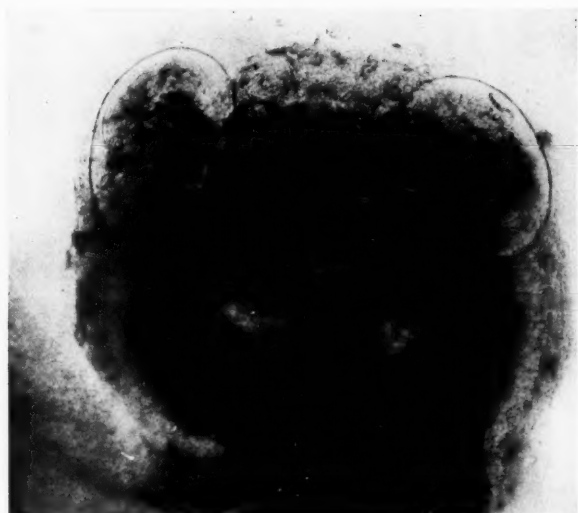
*Case 71.* 1934: patient sprained his ankle, radiograms revealed suspicious shadows, further pictures showed numerous calcified cysts. States that he has never had a fit of any kind. Served in India 1916-18.

Cases 11, 48, 52, 57, 65, 66, and 67 were described by Colonel R. C. Priest in a thesis submitted to the University of Cambridge for the degree of Doctor of Medicine.

We are indebted to Colonel W. Benson, D.S.O., Officer Commanding the Queen Alexandra Military Hospital, for permission to forward these notes for publication.

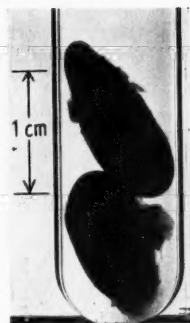
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*a*

(a) *Case 23.* A photomicrograph, low-power  $1\frac{1}{2}$ -inch objective, showing scolex from an excised subcutaneous cysticercus.



*b*

(b) *Case 27.* Photograph ( $\times 2$ ) of two excised subcutaneous cysticerci. The scolex can be seen as a central dark spot.



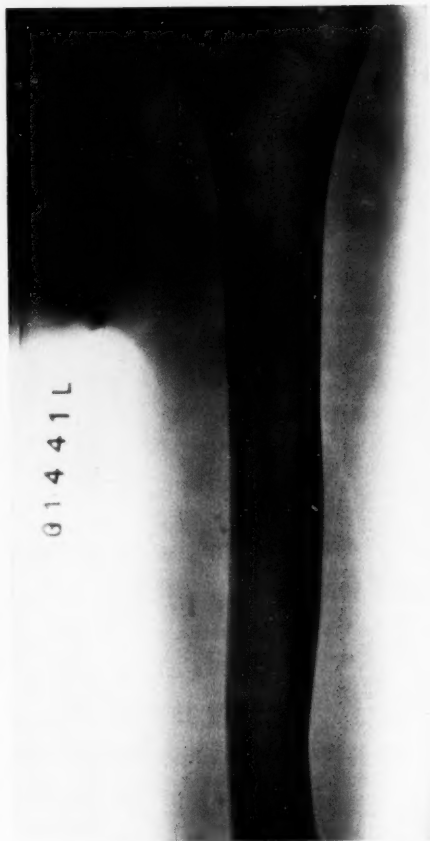
*Case 43.* Photograph, lent by Mr. Hugh Cairns, of section through the brain showing cysticerci mainly in the cortex but also diffusely scattered through the cerebral hemisphere, mostly superficial and within 1.3 cm. of surface. Most of the cysticerci are spherical and measure up to 0.5 cm. in diameter. Sixty-six cysticerci were counted, but there were probably more.





*Case 28. Skiagram. Calcified cysticerci in the brain.*





*Case 29.* Skiagram. Calcified cysticerci showing a comparatively early stage of calcification. Still earlier calcification can be recognized, but is not adapted for reproduction.



*Case 42.* Skiagram. Calcified cysticerci showing the rather larger shadows that may be seen.

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## PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

### TWENTY-EIGHTH ANNUAL GENERAL MEETING

THE TWENTY-EIGHTH ANNUAL GENERAL MEETING was held in Leeds on May 18 and 19, 1934. The meetings were held in the Philosophical Hall. The attendance book was signed by 167 members. The proceedings began at 10 a.m.

*The President*, Professor T. K. Monro, was in the chair.

*The Minutes* of the last Annual General Meeting having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

*Presentation of the Treasurer's Accounts.* Dr. Letheby Tidy presented the Annual Accounts which showed a balance of £209 6s. 5d. The accounts were adopted.

*Selection of Place of Meeting for 1935.* It was unanimously agreed that the next meeting should be held in London.

#### *Election of Officers*

*President.* Professor T. Wardrop Griffith was elected President for 1934-5. On his election he took the Chair, and expressed the thanks of the Association to the Retiring President for his services during the past year.

Election of Members of the Executive Committee, Honorary Member, Foreign Honorary Members, Extra-Ordinary Members, and Ordinary Members followed.

#### *Executive Committee*

*President.* Professor T. Wardrop Griffith.

*Treasurer.* Dr. H. Letheby Tidy.

*Secretary.* Dr. L. J. Witts.

#### *Members for England:*

Sir J. Charlton Briscoe.  
Dr. J. le F. C. Burrow.  
Sir Maurice Cassidy.  
Dr. A. G. Gibson.  
Dr. H. Thursfield.  
Dr. K. D. Wilkinson.

#### *Members for Scotland:*

Dr. D. Campbell.  
Dr. J. Carslaw.  
Dr. J. D. Comrie.

#### *Members for Ireland:*

Dr. L. Abrahamson.  
Dr. Rowland Hill.  
Dr. J. C. Rankin.

#### *Honorary Member:*

Professor T. K. Monro, M.D. (President 1933-4).

*Foreign Honorary Members :*

Lewellys Franklin Barker, Emeritus Professor of Medicine, Johns Hopkins Hospital, Baltimore.

Thomas McCrae, Professor of Medicine in the Jefferson Medical College, Philadelphia.

*Extra-Ordinary Members :*

Dr. F. Craven Moore.

Dr. G. E. Nesbitt.

Dr. R. Barclay Ness.

Dr. F. J. Poynton.

Dr. Lewis Smith.

*Ordinary Members :*

Cyril William Curtis Bain, M.D., Physician, Harrogate Infirmary.

Oscar Brenner, M.D., Physician to Out-patients, Queen's Hospital, Birmingham.

William Sydney Charles Copeman, M.R.C.P., Assistant Physician, West London Hospital.

William Evans, M.D., Physician, Southend General Hospital.

Hector Kenneth Goadby, M.D., Deputy Director, Medical Unit, St. Thomas's Hospital.

Frederick Greig Hobson, M.D., Physician, Radcliffe Infirmary, Oxford.

Philip Henry Manson-Bahr, M.D., Physician, Hospital for Tropical Diseases, London.

Henry Henderson Moll, M.D., Assistant Physician, Leeds General Infirmary.

Charles Edward Newman, M.D., Junior Physician, King's College Hospital.

James Michael O'Donovan, M.D., Professor of Medicine, University College, Cork.

Alan Gordon Ogilvie, M.R.C.P., Assistant Physician, Royal Victoria Infirmary, Newcastle.

Albert Arthur Fitzgerald Peel, D.M., Professor of Medicine, Anderson College, Glasgow.

Thomas Robert Rushton Todd, M.D., Assistant Physician, Royal Infirmary, Edinburgh.

Henry Ashbourne Treadgold, Group Captain, M.D., Consultant in Medicine, R.A.F.

Charles Cady Ungley, M.D., Medical Registrar, Royal Victoria Infirmary, Newcastle.

*Election of an Editor of Quarterly Journal of Medicine.* The President, on behalf of the Executive Committee, recommended the Appointment of Dr. Donald Hunter as Editor of the *Journal*, in place of Dr. Robert Hutchison, who had resigned, and this recommendation was agreed to unanimously.

*Vote of Thanks to Dr. R. Hutchison.* The President moved a vote of thanks to Dr. R. Hutchison for his services to the *Quarterly Journal of Medicine*, pointing out that he was the last of the original editors of the *Journal*. The vote of thanks was passed amid general applause.

*Revision of Rule 15.* The Secretary moved that the words 'one month' in the second sentence of Rule 15 should be changed to 'six weeks' as it had been found in practice that the interval of one month was too short for the work which had to be done between the receipt of the candidates' names and the General Meeting; this was carried.

*Title of Extra-Ordinary Members.* The President reminded Members that at the last Annual General Meeting Sir James Purves-Stewart had raised the question whether the title 'Emeritus Members' would not be more honorific than 'Extra-Ordinary Members' and had given notice that he would move a motion on this matter at the present meeting. The President pointed out that the title of Extra-Ordinary Members had been very fully discussed at the Annual General Meeting in 1929, and on behalf of the Executive Committee he proposed that no change should be made in the title of Extra-Ordinary Members. Sir James Purves-Stewart then proposed, and Professor G. R. Murray seconded, an amendment that the class of members hitherto called Extra-Ordinary Members should be called Senior Members. After some discussion, in which Professors A. J. Hall and Douglas Stanley took part, the amendment was defeated and the President's proposal was carried by a large majority.

*Death of Honorary Member.* Before proceeding to the Scientific Business the President referred to the loss sustained by the Association in the recent death of Professor O. J. Kauffmann.

## SCIENTIFIC BUSINESS

## Friday Morning

1. DR. CLAUDE WILSON epitomized *The Physical Condition of the Everest Climbers of the 1933 Expedition Before and After the Climb*, and alluded also to that of some members of previous expeditions. Most climbers lost about 2 stones of weight on the climb but soon recovered it. None appeared to have deteriorated permanently as a result of the efforts at these great heights. None of those examined after return had enlarged hearts, as determined by X-rays. The most noticeable clinical feature was the slow pulse of the majority of the more successful climbers. The blood-pressure was average or on the low side in most cases, while in one member of the 1924 Expedition, still a very fast climber, it was, in 1934, 100/70, corresponding with his pulse-rate of 48. The electrocardiogram showed a great variety in voltage, some being average, some exceptionally high, while in one case (a very active climber) the voltage was extraordinarily low in all leads before going out, but rather higher after his return. In conclusion the questions of acclimatization, and of the use of oxygen, were briefly discussed.

This communication was discussed by Drs. EDGECOMBE, TIDY, and SPENCE.

2. DR. J. CRIGHTON BRAMWELL referred to a few of the more important clinical findings in a consecutive series of 50 patients exhibiting presystolic *Gallop Rhythm*. From the aetiological standpoint most of these patients could be classified in one of three groups:—(1) Essential hypertension and chronic Bright's disease; (2) coronary occlusion; (3) acute infections of the myocardium. 23 patients had signs of congestive heart failure, but there was not a single example of auricular fibrillation in the series. 37 patients had died, 1 had been lost sight of, and 12 were still alive. 54 per cent. of those suffering from coronary occlusion were still living as compared with 14 per cent. in the other three groups. This was attributed to the transient nature of heart failure in some cases of myocardial infarction. Dr. Bramwell pointed out that the accessory sound and impulse in true gallop rhythm were always associated with auricular systole. When the heart rate was rapid, auricular systole occurred early in diastole. This gave rise to an unusually rapid rate of ventricular filling, and in patients whose ventricular muscle was lacking in tone, produced a sudden distension of the ventricle and set the ventricular walls into vibration. These two phenomena were, in his opinion, responsible for producing the impulse and additional sound characteristic of gallop rhythm.

This communication was discussed by Drs. J. M. H. CAMPBELL, A. G. GIBSON, STACEY WILSON, EVAN BEDFORD, HAMILL, and TRAVERS SMITH.

3. DR. J. COWAN discussed *The Value of Determination of the Electrical Axis of the Heart*, a measure of variations in the preponderance of the right or left sides of the heart, in prognosis. He showed charts illustrating the changes which occurred in progressive heart disease.

DR. H. W. JONES commented briefly on this communication.

4. DR. JOHN PARKINSON and DR. CLIFFORD HOYLE gave a joint communication on *Thyrotoxic Hypertension*. In a brief review of present knowledge concerning the effect of thyroid toxæmia on the cardiovascular system, Dr. Parkinson drew special attention to a group of patients with hypertension in whom there were ruling features of thyrotoxic origin. A raised basal metabolic rate was not a crucial test in such cases, for the metabolism might be increased from hypertension or heart failure only. Clinical evidence was sufficient when general thyrotoxic signs were accompanied by a goitre, and especially if auricular fibrillation supervened. Dr. Hoyle then gave an analysis of 100 cases of thyrotoxic hypertension, emphasizing the preponderance in females and the frequency of long-standing goitre, which was often disregarded or even denied. The high incidence of nervousness, wasting, tachycardia, and auricular fibrillation—i.e. the thyrotoxicosis—in these patients with hypertension justifies their separation into a special group for purposes of prognosis and treatment.

This paper was discussed by Drs. COWAN, HAY, STACEY WILSON, G. R. MURRAY, FRASER, and K. D. WILKINSON.

5. DR. WILLIAM EVANS discussing *Syphilitic Angina Pectoris* said that syphilis was a common cause of angina, and the favourable response met with in certain cases

from treatment with mercury and iodide called for early diagnosis of the condition. Angina due to syphilis was never present unless some degree of stenosis of the coronary orifices had been produced. Aortic incompetence was common in syphilitic angina, but the mechanical effect of superadded aortic regurgitation did not increase the incidence of angina in syphilitic aortitis. Recovery from myocardial infarction in syphilitic aortitis probably never takes place. Enlargement of the heart in syphilitic angina pectoris results from the presence of aortic incompetence or a raised blood-pressure.

6. PROFESSOR ARTHUR ELLIS reported eleven cases of *Periarthritis Nodosa*, three of which he had seen during life, the remainder collected from the records of the London Hospital. The disease usually presents itself as a pyrexia of unknown origin; this was the case in 6 of the 11 cases in the series. Enteric fever and disseminated tuberculosis are the conditions most commonly suspected. Though preceding muscular pains are common, abdominal pain is the most important early symptom. It was the chief complaint on admission in 7 patients, and was responsible for the initial diagnosis of appendicitis in 2 instances. The patients usually complain also of weakness and prostration. The pyrexia is only slight or moderate in degree; it is of irregular type with well-marked diurnal variation. The pulse is often more rapid than the fever would justify. There is usually a well-marked leucocytosis, which may exceed 20,000, the differential count being of inflammatory type. Cerebral symptoms such as mental apathy and depression, with tearfulness and melancholia, or even mild mental derangement, are not uncommon. The disease may simulate a peripheral neuritis. Subcutaneous nodules may occur, and histological examination of these is the commonest source of diagnosis during life.

Little time was available for the discussion of this important paper, but DRS. HARDY and STOTT made brief comments.

7. PROFESSOR A. J. HALL showed a cinematograph film illustrating certain features of *Bell's Phenomenon*. Attention was called to the biphasic nature of the acts of closing and opening the eyes, each consisting of a palpebral and a global phase: also to the three types of upward movement in the global phase. In a large series of normal persons these were present in the following proportion:—

Type I.	Upward movement maximal	60 per cent.
Type II.	Upward movement medium	25 per cent.
Type III.	Upward movement minimal	15 per cent.

In Type III, there is no appreciable upward movement on closure, sometimes indeed the eye turns down. This is the so-called inverted Bell's Phenomenon.

2 p.m. to 3 p.m.

Demonstration of Clinical Cases in the Leeds General Infirmary.  
Physiological and Pathological Demonstrations in the Medical School.

### 3 p.m. Afternoon Session

1. DR. O. LEYTON reported that *Continuous Injection of Insulin* subcutaneously or intravenously, did not appear to control the sugar content of the blood any more satisfactorily than subcutaneous injections at intervals of four hours. The great improvement following these injections (an improvement often temporary) seemed to be due to the withholding of fat and protein rather than to the continuous presence of insulin in the circulating blood for a period.

This communication was discussed by PROFESSOR ELLIS.

2. DR. S. W. PATTERSON reported three cases of *Thyroid Addiction*. Two of these cases, women, were severe; one had taken thyroid in large doses intermittently for at least 3½ years, the other continuously for over five years. All three patients had symptoms due to excessive thyroid intake.

DRS. JOHN HAY and G. R. MURRAY made brief comments.

3. PROFESSOR HENRY COHEN and PROFESSOR J. H. DIBLE reported the case of a female, aged 52 years, who had been under observation for two years with the typical clinical picture of *Pituitary Basophilism* described by Harvey Cushing, and who was found at autopsy to have a basophil adenocarcinoma of the anterior lobe of the

pituitary body with liver metastases; slight changes in the suprarenal cortex were the only accompanying endocrinous features.

DR. PARKES WEBER, A. P. THOMSON, and CHARLES took part in the discussion.

4. DR. IVY MACKENZIE spoke on *Unusual Forms of Cerebral Venous and Arterial Thrombosis*. Two cases of acute venous thrombosis, followed by delirium and death in three weeks, presented no physical signs before death pointing to the diagnosis. In one case the superior longitudinal sinus and related veins on the surface and the vein of Galen were thrombosed; in the other, occipito-parietal veins and the vein of Galen; in both there were diffuse haemorrhages in the white matter and basal nuclei, but no microscopic evidence of encephalitis. A case of chronic arterial thrombosis of cerebral vessels extending over three years, with true bone formation in the thrombi, was also reported. There was no bone formation in the vessel walls, but the glistening bone of the thrombi could be seen in the small superficial cerebral arteries.

DR. F. R. FERGUSON discussed this communication.

5. DR. A. R. PARSONS described *An Acute and Rapidly Fatal Nervous Lesion* in a healthy-looking, well-developed woman, aged 32 years, who was carried into hospital with loss of power in all her extremities. She had been ill with bronchitis for two weeks and had a temperature of 101° F. She suddenly lost power in her right arm, and in the course of the next three days all four limbs were completely paralysed except for slight movement by the toes. Paralysis was flaccid, deep reflexes abolished, no marked sensory symptoms or wasting. On admission she had full control of the bladder and rectum, the urine was normal, and the abdominal reflexes were present though they could not be elicited 48 hours later. Respiration became difficult and she died from cardiorespiratory failure four days after admission. On post-mortem examination (Dr. Lait) the bronchioles were plugged with purulent secretion with surrounding broncho-pneumonia, the cerebrospinal fluid was sterile. Cross-sections of the cord showed congestion, haemorrhages, and infiltration of plasma cells; the anterior horn cells were extensively involved, shrunken and distorted, with disintegration of processes and axis cylinders and phagocytosis and chromatolysis of the anterior horn cells. Death was due to broncho-pneumonia with acute anterior poliomyelitis.

DRS. G. R. MURRAY, PARKES WEBER, GARLAND, and IVY MACKENZIE took part in the discussion.

6. DRS. LESLIE COLE and E. C. T. SPOONER (introduced) described *The Results of Treatment of 17 Cases of Tetanus*. In most, a single dose of 200,000 International units of antitoxin was given intravenously. The fate of injected antitoxin was investigated in 4 such cases, and these experiments indicated a general correspondence in rates of disappearance of protective power and showed that after 14 days there still remained from 3 to 6 units of antitoxin per c.c. of serum. The value of full doses of avertin for controlling the spasms was confirmed and rectal paraldehyde was also found to be useful. Curare was used with advantage in one severe case which recovered, 256 mg. being given subcutaneously at intervals over a period of 7 days. As much food as possible was given in all cases. Results:—Under 42: 14 cases, 10 recovered; over 60: 3 cases, all fatal.

DRS. RYLE, TIDY, ELLIS, and K. D. WILKINSON discussed this communication.

7. DR. J. W. McLEOD discussed the *Significance of Bacterial Types in Diphtheria* with an analysis of 2,329 cases. 'Gravis' infection in 947 cases shows a 13.7 per cent. death-rate and a definite tendency to epidemic incidence. 'Intermediate' infection in 906 cases shows an 8.5 per cent. death-rate and less tendency to epidemic incidence. 'Mitis' infection in 428 cases shows a 3.3 per cent. death-rate and sporadic incidence. 41 atypical strains were found in this series and 7 double infections. The 'gravis' strains are the most constantly pathogenic to animals. They also predominate in the small series of authentic cases of diphtheria occurring in Shick negative individuals in which the bacterial type has been determined.

The Annual Dinner was held at the Queen's Hotel. The President, Professor T. Wardrop Griffith, was in the chair. The official guests included the Vice-Chancellor of Leeds University, the Dean of the Faculty of Medicine, the Chairman of the Infirmary Board, and Mr. Charles Lupton. 137 Members and Guests were present.

## Saturday Morning

1. DR. F. PARKES WEBER discussed the *Clinical Syndrome of Cystic Dilatation of the Common Bile Duct*, illustrating his remarks by the case of a little girl in whom the correct diagnosis was not arrived at before the post-mortem examination, though the presence of hepatic cirrhosis had been recognized 3½ years previously. He suggested that such cases should be called 'idiopathic megalocholedochus' to stress the analogy with megaloesophagus (idiopathic dilatation of the oesophagus) megalocolon (Hirschsprung's disease), and megalureter (idiopathic dilatation of the ureters). In the clinical diagnosis of megalocholedochus the great point was to think of its possible existence in every case of intermittent or remittent obstructive jaundice—with or without pain, evidence of hepatic cirrhosis, &c.—especially in young girls.

DRS. HURST, MCNEE, and L. G. PARSONS made brief comments.

2. DR. T. C. HUNT showed the results of *Biliary Drainage* in 100 cases, including 32 normal subjects. The rate of flow of the bile was of no value in diagnosis, but pain and nausea during the flow occurred in 75 per cent. of gall-stone cases. Complete failure to obtain bile was rare and suggested gall-bladder dyskinesia. Absence of concentrated 'B' bile occurred in 10 per cent. of normals and 75 per cent. of pathological gall-bladder cases. In association with a normal cholecystogram it was characteristic of liver disease. The finding of pigment and cholesterol crystals together was noted in 20 per cent. of normals and 77 per cent. of gall-stone patients.

This communication was discussed by DRS. HURST, NEWMAN, and MCNEE.

3. DR. HUGH BARBER gave an account of five workmen who died in 1933 from *Necrosis of the Liver and Nephritis from Industrial (Dioxan) Poisoning*. The chemical toxin was absorbed by inhalation. A few intensive exposures were more serious than repeated slight ones. The kidneys showed haemorrhagic necrosis in the cortex, which resulted in suppression of urine and uraemia. A large pale liver revealed, on histological examination, widespread zonal necrosis. The duration of the fatal illness was from five to eight days.

Brief comments were made by DRS. MCNEE, STOTT, and PARKES WEBER.

4. DR. H. S. PEMBERTON discussed the *Value of Gold in the Treatment of Chronic Arthritis*. After reference to types of gold salts available, dosage and toxicity, he described the results in 70 selected cases, some of which had been under observation for 4 years after gold treatment. In all, 82 per cent. showed improvement: of these 9 were cured, 17 much improved, and 32 improved. Such factors as changes in carbohydrate tolerance, gastric acidity, focal sepsis, &c., did not appear to influence the treatment, which he thought was of value even in osteo-arthritis.

DR. PARKES WEBER discussed this communication.

5. DR. C. W. BUCKLEY reported three cases of *Tuberculous Polyarthritis* in which tubercle bacilli had been found in the joints, and referred to others in the literature. In his cases there was no sign of active tuberculosis elsewhere and this was evidence that the tubercle bacillus was a possible cause of chronic polyarthritis, but the discovery of the bacillus in the joints or the blood could not be accepted as indicating the cause of the arthritis if there was any active focus elsewhere in the system. The type of arthritis, ankylosing or otherwise, was dependent on constitutional or environmental causes rather than on the bacterial factor.

DR. PARKES WEBER also spoke.

6. DR. R. D. PASSEY (introduced) considered the *Reported Rise in Intrathoracic Cancer* as possibly more apparent than real. Most writers deal only with the percentage incidence in *post mortems*. This is open to serious fallacy as only 55 per cent. of those dying in 16 teaching hospitals of Great Britain undergo necropsy. That consultants to-day undoubtedly see more cases than formerly does not necessarily indicate a real increase in incidence. Improvement in diagnosis of all chest conditions, tuberculosis legislation, free medical benefit, and general ageing of the population might easily account for more cases being recognized and sent for consultation.

This paper aroused much interest and criticism and was discussed by DRS. TIDY, K. D. WILKINSON, CHANDLER, PARSONS, PARKES WEBER, MURRAY, and M. DAVIDSON.

7. DRS. M. J. STEWART and E. S. FOWWEATHER (introduced) discussed the *Silica Content of Silicotic Lungs and its Bearing on Silicosis*. They showed that there is no close connexion between the total amount of silica present and the degree of silicotic fibrosis. Hence silicosis must be due to either the nature of siliceous material inhaled, or to some conditions present in the lungs to which the material gains access. Variations in individual resistance and Kettle's work on the infective factor present in the lungs were referred to. Variations in trades and therefore in response to different dusts were pointed out, and W. R. Jones's work on fibrous silicates, chiefly cercite, was mentioned. 2 cases of special interest were described, and it was suggested that silicosis is due to chemically active silica.

2 p.m. to 3 p.m.

Demonstration of Clinical Cases at the General Infirmary.

Physiological and Pathological Demonstrations in the Medical School.

3 p.m. Afternoon Session

1. DR. A. GOODALL showed lantern slides illustrating a case of *Pre-Leucocythaemic Cutaneous Chloroma*. Round, dark-red patches surrounded by a zone of bright green appeared over the trunk, with a few on the face. The largest measured  $2\frac{1}{2}$  in. in diameter. Sections showed a great infiltration with cells resembling lymphocytes. The white-cell count never exceeded 8,800. After a very moderate exposure to X-rays the patches disappeared, and the leucocyte count fell to 400 per cu. mm., with 30 per cent. of myeloblasts and myelocytes. Orchitis then developed, and after a week of high fever the patient died. Post-mortem examination revealed a severe and universal infection by *B. coli*. The changes in the organs were those of early granular leukaemia with an active marrow. This made the leucopenia the more remarkable.

2. DRS. J. W. MCNEE and J. MCMICHAEL (introduced) described *Three Cases of Chronic Splenomegaly* in which great splenic enlargement, up to  $9\frac{1}{2}$  lb., due to myeloid metaplasia, occurred in adult women. The blood picture was leuco-erythroblastic: white-cell counts ranged from 2,000 to 60,000 with 3 to 25 per cent. myelocytes, while the red-cell count varied from 2 to 6 million with erythroblasts comparable in numbers to the myelocytes. Great fluctuations occurred in the haematological features. The liver became enlarged later; death occurred 4 to 5 years after with purpuric manifestations. Splenectomy and X-rays were of no value. Associated bone disease was excluded in the only case which came to autopsy.

These cases were discussed by DRS. HURST, HICKLING, D. HUNTER, A. R. PARSONS, and TIDY.

3. DR. TERENCE EAST described a group of cases in which *A Form of Acholuric Jaundice* was present without excessive fragility of the red cells. Some were members of a family which recorded jaundice for at least three generations. In four members of this family no abnormal fragility of the red cells had ever been found. There was a tendency to anaemia with high-colour index. The jaundice increased on illness. Splenectomy in one case with severe anaemia improved the blood count, but this patient still had jaundice. 2 cases had no family history. One had a very large spleen without much anaemia; the fragility of the red cells was normal, and removal of the spleen cleared up the jaundice. In another, severe anaemia and jaundice were relieved by splenectomy.

This communication was discussed by DR. WARNER, PARKES WEBER, THOMSON, and TIDY.

4. DR. S. J. HARTFALL (introduced) reported a number of cases of *Idiopathic Hypochromic Anaemia* in which daily feeding of yeast, pepsin, and hydrochloric acid, incubated for  $2\frac{1}{2}$  hours, caused a small reticulocyte crisis and a rise in haemoglobin percentage. The diet and iron intake were unchanged throughout. The rise in haemoglobin percentage, being unaffected by the small iron content of yeast, was attributed to some influence increasing iron absorption. Clinical trials with yeast and Bemax alone, or with the addition of hydrochloric acid and pepsin, only occasionally raised the haemoglobin. Combined vitamin B rich feeding with inorganic iron salts gave no better result than optimal doses of iron alone. Vitamin B<sub>1</sub> and B<sub>2</sub> had no

effect on haemoglobin. The original results appeared to depend upon some unidentified product of peptic digestion of yeast.

This paper was discussed by Drs. UNGLEY and L. G. PARSONS.

5. Drs. R. A. VEALE and R. E. TUNBRIDGE (introduced) referred to two cases of *Idiopathic Steatorrhoea* and pointed out the striking variability in the order of appearance of symptoms. The results of treatment in these cases were discussed. In both the anaemia was of the megalocytic hyperchromic variety but there was no response to marmite. The importance of a fat-free diet was stressed.

There was an interested discussion of this paper, in which Drs. MANSON-BAHR, DONALD HUNTER, L. G. PARSONS, and J. F. WILKINSON joined.

6. Drs. F. J. NATTRASS and C. C. UNGLEY showed a cinema film illustrating the *Treatment of 20 cases of Subacute Combined Degeneration of the Spinal Cord by the Injection of Campolon Intramuscularly*, 18 to 42 c.c. a week for 9 to 46 weeks. Paraesthesiae, mental and sphincter disorders, dysfunction of hands, Romberg's sign and inco-ordination, improved consistently; vibration and joint sense less so. Absent knee-jerks often returned; ankle-jerks rarely. Increased jerks showed little change, and extensor plantar reflexes became normal in a few.

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